IM03-16-03

Surge Dose® ketamine as an oral analgesic and sedative agent

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1 Executive Summary

Imaginot's active ultra-rapid Surge Dose® dissolution technology produces fast dissolving tablet formulations which reduce in vivo dissolution times under the wide range of gastric conditions encountered in the general population. Surge Dose® formulations exhibit absorption profiles more closely resembling solutions than conventional passively dissolving tablets, with drugs typically absorbed more rapidly from solutions than from solid dosage forms. Optimised Surge Dose® tablets achieve rapid in vivo dissolution so that dissolved drug rapidly reaches the small intestine and higher concentrations of dissolved drug drive fast absorption. This results in higher plasma concentrations to drive distribution with faster onset of action and achievement of peak effect.

Faster in vivo dissolution also reduces inter- and intra-subject PK (pharmacokinetic) variability resulting from inconsistent and slow in vivo dissolution. Where peak plasma levels are around minimum therapeutic plasma levels, improved, more consistent absorption in a higher proportion of subjects can lead to greater efficacy. Hence Surge Dose® formulations have the potential to improve therapeutic outcomes by reducing the frequency of low and possibly sub-therapeutic, peak plasma concentrations. In contrast, conventional formulations relying on slow, passive dissolution in vivo where stagnant boundary layers around drug particles slow dissolution, achieve slower and less consistent absorption with lower plasma concentrations.

Ketamine <Ketalar® (Pfizer)> is a N-methyl-D-aspartate (NMDA) receptor antagonist primarily administered parenterally as a non-barbiturate anaesthetic especially for short term procedures and the induction of anaesthesia. Although the only products registered to date are injectable solutions, there is increasing oral use of the drug for analgesia and sedation. As no solid dosage forms of ketamine are currently registered, this presents an opportunity for the development and registration of a Surge Dose® ketamine tablet which offers fast absorption approaching that of a solution without the inconvenience and palatability issues of the current injectable solutions. In these indications, faster and more consistent onset of action than other conventional products is a significant clinical and commercial advantage.

Although ketamine has low oral bioavailability around 10 - 20 % as a result of first-pass hepatic metabolism, it is converted to an active metabolite norketamine which contributes to the efficacy and avoids the adverse effects of higher ketamine levels seen after parenteral administration. Effective oral analgesic doses are in the range 25 – 250 mg,

This review indicates that ketamine is a suitable Surge Dose® candidate against the key criteria of solubility, permeability and PK-PD (pharmacodynamic) correlation. Ketamine is

a BCS Class 1 drug which suggests that application of Imaginot's Surge Dose® technology will provide clinical benefits compared with conventional tablet formulations:

(i) **High aqueous solubility** – A base with a pKa of 7.5, ketamine is highly soluble in water around 250 mg/mL so that doses of up to 500 mg will dissolve completely in liquid volumes available in vivo, and solubility will not be dissolution or absorption rate limiting. Although more soluble in acidic conditions, the higher proportion of drug in the unionised form under alkaline conditions where solubility is lower, will favour absorption.

(ii) **High intestinal permeability** – Ketamine has high passive permeability with no P-glycoprotein mediated efflux so there will be no rate limitation for intestinal transmucosal absorption.

(iii) **Good PK-PD correlation** – Following oral administration, onset of action is around 30 minutes corresponding to peak plasma levels demonstrating a close correlation between plasma concentrations and PD effects. Although analgesia is associated with lower plasma levels or around 40 ng/mL after oral administration compared to above 100 ng/mL when injected, these lower levels are associated with high levels of the active metabolite norketamine produced by first pass hepatic metabolism. Ketamine is rapidly distributed from the plasma with a short $t_{1/2}$ of 7 - 11 minutes.

A robust and stable Surge Dose® tablet formulation of ketamine has been developed under an agreement with a French pharmaceutical company, Ethypharm SA. This optimised Surge Dose® ketamine tablet demonstrated ultra-rapid in vitro dissolution under a variety of conditions, significantly faster than conventional tablets.

A PK-PD study was planned comparing Surge Dose® ketamine with solution and conventional tablets in healthy volunteers using non-invasive PD measures such as sedation and analgesia. Unfortunately the project was deferred as a result of the high clinical costs to register an oral form of ketamine for analgesia.

Since fast in vivo dissolution will deliver the drug to the site of absorption already in solution, Surge Dose® ketamine tablets will achieve faster and more consistent absorption leading to faster onset of action and improved efficacy following oral administration when compared to traditional oral solid dosage form technologies. A Surge Dose® ketamine tablet is expected to provide a superior oral product compared with conventional tablets with T_{max} values less than 30 minutes and a correspondingly fast onset of action, in the region of 10-15 minutes for sedation and 20-30 minutes for analgesia. More consistent absorption should allow the use of lower doses which will minimise the potential for side effects without compromising efficacy.

2 Background

Imaginot has developed its fast dissolving fast absorbed Surge Dose® technology based on in vitro dissolution testing of a wide range of drugs, and in vivo evaluation of paracetamol tablets. Ultra-rapid in vitro dissolution is associated with fast in vivo absorption as demonstrated in Imaginot's proof of concept clinical trial in 25 fasted subjects where absorption of paracetamol from two preliminary Surge Dose® formulations was faster than from two commercial products with good in vitro in vivo correlations (IVIVC)[1].

From the nineteen PK studies completed during the development of the Surge Dose® technology, Imaginot found that products with fast in vitro dissolution generally resulted in a higher frequency of fast absorption occasions based on plasma concentration - time profiles. Each fast absorption occasion was associated with higher peak plasma concentrations (C_{max}) compared with slow absorption occasions. Imaginot has demonstrated that slow absorption can lead to a high proportion of low C_{max} and that for paracetamol, many of these low concentrations are sub-therapeutic being below documented minimum therapeutic plasma levels of 10 mg/mL.

Paracetamol is a well recognised marker of gastric emptying, and these studies clearly demonstrated the effect of the different phases of gastrointestinal motor activity known as the Migrating Motility Complex (MMC) on absorption. This explains the variability seen with many drugs, even when administered in solution, and highlights the importance of achieving ultra-rapid in vivo dissolution of drug from a solid dosage form to minimise variability and achieve a higher frequency of fast absorption profiles.

Surge Dose® formulations provide active ultra-rapid dissolution ensuring that in vivo dissolution times are minimised under the wide range of gastric conditions encountered in the general population. Since liquids empty exponentially from the stomach with a half life of around 5 - 22 minutes[2], the resultant solution produced in vivo quickly enters the small intestine whence it is absorbed. Fast absorption and higher concentrations of dissolved drug to drive distribution, lead to improved therapeutic outcomes through faster onset of action and greater efficacy as a result of more consistent absorption rapidly exceeding minimum effective plasma concentrations.

In contrast, conventional tablet formulations undergo relatively slow passive dissolution as the stagnant boundary layers around the dissolving drug particles effectively retard

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1 Imaginot Pty Ltd. Pharmacokinetics of paracetamol formulations IM0401, Nov 2005

2 Oberle RL, Chen TS, Lloyd C, Barnett JL, Owyang C, Meyer J, Amidon GL. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroenterology* (1990) **99**(5):1275-1282

dissolution. This results in slower and more variable absorption with slower and more variable onset of action.

If a formulation is able to drive drug dissolution in the co-administered water, a high concentration of dissolved drug will empty from the stomach and drive absorption through the intestinal mucosa resulting in high plasma concentrations. In such cases, the absorption profile for the ultra-rapid dissolving tablet will be closer to that for a solution than a conventional tablet where only partial dissolution occurs in the stomach. A lower concentration of dissolved drug provides less of a driving force for passive diffusion across the intestinal wall leading to slower absorption and lower C_{max} which may even be sub-therapeutic for some drugs.

The solubility of many drugs is influenced by pH, and Surge Dose® tablets are designed to achieve ultra-rapid dissolution under the wide range of physiological gastric conditions which exist. These include acidic (low pH) to neutral conditions (around pH 7), as well as lack of gastro-intestinal motility such as in gut stasis associated with migraine.

- Acidic drugs have low solubility at low pH, so acidic conditions in the stomach will limit solubility and can delay dissolution with correspondingly slower absorption. However if gastric conditions are less acidic, such as in the presence of food or if gastric secretions are otherwise depressed or neutralised, a higher pH will favour solubility and enhance dissolution for acidic drugs.
- Conversely, basic drugs have higher solubility at low pH and reduced solubility at higher pH, so solubility and dissolution will be favoured under acidic gastric conditions. If gastric contents are neutralised to any degree, then the higher pH will tend to limit solubility and slow dissolution of basic drugs.

Surge Dose® formulations are optimised for each drug to enhance its solubility and provide active dissolution for ultra-rapid dissolution in the stomach under all physiological conditions, independent of gastric pH and gastrointestinal motility.

Ideally suitable Surge Dose® candidates have:

- sufficient solubility under physiological pH such that the total dose of the drug will dissolve in the limited volumes of fluid typically available in vivo
- good oral bioavailability absorbed by passive diffusion from the small intestine
- good correlation between PK and PD profiles

Surge Dose® formulations of suitable candidates will achieve ultra-rapid dissolution in vivo which is likely to lead to:

- rapid absorption and more rapid onset of peak effect

- a reduction in slow absorption occasions, which lead to low, possibly sub-therapeutic, plasma concentrations

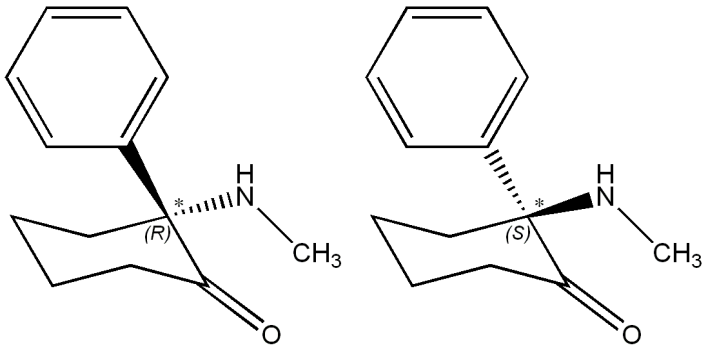
This report was prepared to assess the feasibility of ketamine as an orally administered analgesic and sedative agent in a rapidly dissolving Surge Dose® tablet formulation.

3 Ketamine

3.1 Physicochemical properties

The molecular weight (MW) of ketamine hydrochloride (HCl) is 274.2 and that of the free base ketamine is 237.7. This molecule contains a chiral centre with two resolvable optical isomers as shown in Figure 1. The S-form has around four times greater affinity for the NMDA receptor than the R-form. Ketamine HCl is a white crystalline powder with a melting point of 262-263 °C.

Figure 1 Molecular structure of ketamine



(*R*)-Ketamine **(*S*)-Ketamine**

As ketamine HCl is an acidic salt of a weak base with a pKa of 7.5, more than 50 % of the drug will be ionised in solution in the physiological pH range. Higher pH values, as found in the small intestine, will favour absorption of the unionised form.

This drug is freely soluble in water, around 1 in 4, such that a 10 % solution is slightly acidic with a pH of 3.5 – 4.1. While no data have been found on the effect of pH on solubility, it is likely that, as for other bases, the solubility will decrease as the pH increases.

The Biopharmaceutical Classification System (BCS)[3] defines a highly soluble drug as one where the Dose Number (D_0) is less than 1 where $D_0 = M_0 / (V_0)(C_s)$. For ketamine, assuming the highest dose (M_0) is 500 mg, the solubility (C_s) is 250 mg/mL, and if the

[3] US DHHS FDA CDER (2000) Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a Biopharmaceutics Classification System.

minimum volume available in vivo for drug dissolution (V_0) is 250 mL, D_0 will be 0.008. This value is below the limit of 1 which means that ketamine meets the criterion for a highly soluble drug in relation to its bioavailability.

3.2 Absorption, distribution, metabolism and elimination

Ketamine is rapidly and extensively distributed throughout the body, readily crossing the blood-brain barrier. The mean volume of distribution ranges from 1 – 3 L/kg with a distribution $t_{½}$ of 7 – 11 minutes. It is approximately 20 – 50 % bound to plasma proteins.

Although ketamine is readily and completely absorbed from the small intestine when administered orally, it undergoes extensive first-pass hepatic metabolism by cytochrome P-450 enzymes resulting in its lower oral bioavailability of around 10 – 20 %. N-dealkylation produces norketamine, the major active metabolite which is formed at similar concentrations to the parent compound and has approximately one-sixth the potency of the parent drug. Other metabolites are formed by hydroxylation of the cyclohexone ring and conjugation with glucuronic acid and dehydration of the hydroxylated metabolites to form the cyclohexene derivative.

The active metabolite norketamine appears to contribute to the antinociceptive effects of oral ketamine through its NMDA receptor antagonist activity, reducing sensitivity to painful stimuli. In rats, the average concentration ratio of norketamine to ketamine was 6.4 for plasma and 2.9 for brain tissue indicating distribution of the active metabolite to the brain[4]. Spinal norketamine was approximately equipotent to ketamine.

After IV administration, bi- or tri-exponential elimination occurs. The first phase represents the anaesthetic action followed by redistribution from the CNS to the peripheral tissues and hepatic metabolism to the active metabolite norketamine. The alpha phase lasts around 45 minutes with a $t_{½}$ of 10 – 15 minutes; the beta phase $t_{½}$ is around 2.5 hours. Some 90 % of the drug is excreted in the urine, with only 2 – 4 % as the unchanged drug.

3.3 Products

Ketamine HCl has been marketed since 1970 as Ketalar® injection <Pfizer>[5] available in 5, 10 and 50 mL vials containing ketamine HCl where 1.15 mg is equivalent to 1 mg of the base. The drug is formulated as a slightly acidic solution (pH 3.5 – 5.5) in concentrations containing the equivalent of 10, 50 or 100 mg ketamine base per mL.

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4 Shimoyama M, Shimoyama N, Gorman AL, Elliott KJ, Inturrisi CE. Oral ketamine is antinociceptive in the rat formalin test: role of the metabolite, norketamine. *Pain* (1999) **81**:85 - 93

5 Prescribing Information Sheet. Ketalar®, Monarch Pharmaceuticals, Inc, Bristol, TN 37620, USA. Issued April 2004. 5 pages

Benzethonium chloride is used as a preservative at up to 0.1 mg/mL. When stored below 30 °C the injectable solution has a 2 year shelf life indicating that the molecule has good chemical stability in aqueous solution.

Although there is increasing use of ketamine orally for analgesia and sedation, no solid dosage form has been registered in major markets. While the injectable solution has been administered orally, it must be mixed with drinks such as cola, sour cherry or orange juice to mask the bitter taste. A solid dosage form would be much more convenient and palatable for regular oral use in the home setting.

3.4 Therapeutic use

3.4.1 Parenteral administration

Ketamine is a non-barbiturate dissociative anaesthetic administered intramuscularly (IM), or intravenously (IV) as a bolus or infusion, to induce and maintain anaesthesia. Onset of action is rapid with 2 mg/kg IV producing surgical anaesthesia within 30 seconds of the injection and effects lasting 5 – 10 minutes. However its clinical usefulness is limited by cardio-vascular stimulant effects and a relatively high incidence of disturbing emergence reactions such as vivid dreams, sensory distortions and hallucinations[6].

At sub-anaesthetic doses, ketamine has analgesic properties believed to be mediated through inhibition of the N-methyl-D-aspartate (NMDA) receptor gated calcium channel. Prolonged stimulation and sensitivity of the NMDA receptors may lead to toxicity of inhibitory inter-neurones which interferes with the pain severity modulating process.

3.4.2 Oral administration

Ketamine is increasingly being used orally as an analgesic and sedative agent at doses from 100 to 500 mg daily in divided doses[7, 8]. Oral administration is much more convenient for regular use especially in the treatment and management of pain in the domestic rather than hospital setting.

Hence a fast dissolving Surge Dose® tablet will conveniently provide the benefit of fast absorption allowing the use of the lowest possible dose and minimising the potential for adverse side effects.

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6 Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Pall Care Pharmacother* (2002) 1**6**(3):7 - 35

7 White, PF, Way WL, Trevor AJ. Ketamine – its pharmacology and therapeutic uses. *Anesthesiology* (1982) **56**:119-136

8 Kapur N, Friedman R. Oral ketamine – a promising treatment for restless legs syndrome. *Anesthseia & Analgesia* (2002) **96**(4):1238 - 9

3.4.2.1 Analgesia

Oral ketamine is reported to produce effective analgesia in a wide range of different conditions. [9,10, 11,12, 13, 14, 15,16, 17]. Recommended oral doses start with a dose of 0.5 mg/kg at bedtime to minimize the likelihood of side effects, increasing by 0.5 mg/kg as tolerated until pain relief is achieved or until side effects occur [18]. The mean effective dose was 200 mg/day. Lower oral doses avoid some of the psychotomimetic adverse effects and dose-dependent cardiovascular stimulation seen with parenteral use.

Oral doses ranging from 25 to 100 mg 6 – 8 hourly to a single 250 mg dose at bedtime produce effective analgesia. In a 31 year old male with advanced AIDS and peripheral neuropathy, SC infusion was effectively replaced with 50 mg increasing to 200 mg orally every 8 hours, although the higher dose was associated with vivid dreams. A second patient was maintained pain free without adverse effects by increasing the dose from 25 mg 8 hourly to 100 mg 6 hourly. A 54 year old woman with refractory fibromyalgia and severe post-traumatic neuropathic pain was effectively controlled for 9 months with 250 mg oral ketamine at bedtime without any side effects [19].

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9 Villanueva-Perez VL, Cerda-Olmedo G, Samper JM, Minguez A, Monsalve V, Bayona MJ, De Andres JA. Oral ketamine for the treatment of type I complex regional pain syndrome. *Pain Pract* (2007) **7**(2):206 - 7

10 Heidari SM, Saghaei M, Hashemi SJ, Parvazinia P. Effect of oral ketamine on the postoperative pain and analgesic requirement following orthopedic surgery. *Acta Anaesthesiol Taiwan* (2006) **44**(4):211 - 5

11 Sakai T, Tomiyasu S, Ono T, Yamada H, Sumikawa K. Multiple sclerosis with severe pain & allodynia alleviated by oral ketamine. *Clin J Pain* (2004) **20**(5):375-6

12 Fitzgibbon EJ, Hall P, Schroder C, Seely J, Viola R. Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: a strategy for conversion from parenteral to oral ketamine. *J Pain Symptom Manage* (2002) **23**(2):165 - 70

13 Vick PG, Lamer TJ. Treatment of central post-stroke pain with oral ketamine. *Pain* (2002) **92**(1-2):311 - 3

14 Fisher K, Hagen N. Analgesic effect of oral ketamine in chronic neuropathic pain of spinal origin – a case report. *J Pain Symptom Manage* (1999) **18**(1):61-6

15 Nikolajsen L, Hansen PO, Jensen TS. Oral ketamine therapy in the treatment of postamputation stump pain. Acta *Anaesthesiol Scandy* (1997) **41**(3):427-9

16 Broadley KE, Kurowska A, Tookman A. Ketamine injection used orally. *Palliat Med* (1996) **10**(3):247-50

17 Hoffman V, Coppejans H, Vercauteren M, Adriaensen H. Successful treatment of postherpetic neuralgia with oral ketamine. *Clin J Pain* (1994) **10**(3):240-2

18 Hocking G, Cousins MJ. Ketamine in chronic pain management: An evidence-based review *Anesth Analg* (2003) **97**: 1730-1739

19 Oye I, Rabben T, Fagerlund TH. [Analgesic effect of ketamine in a patient with neuropathic pain]. [Norwegian] *Tidsskrift for Den Norske Laegeforening* (1996) **116**(26):3130-1

A group at the Institute Rotary Cancer Hospital in New Delhi reported that low dose oral ketamine (0.5 mg/kg) in addition to existing drug regimens was beneficial and effective in the management of neuropathic pain in patients with advanced cancer based on pain, sedation and vomiting scores[20].

Oral ketamine 100 mg daily in divided doses, increasing the dose by 40 mg daily until analgesia was achieved or side effects became limiting was studied in 21 patients with neuropathic pain. While 9 patients withdrew because of side effects, and 4 patients received no benefit, others continued to take 100 – 240 mg daily, with one patient taking 500 mg/day without side effects for more than one year[21].

Low dose oral ketamine at a dose of 0.5 mg/kg 12 hourly was an effective co-adjuvant analgesic in 60 patients with cancer pain demonstrating an opioid tolerance-sparing effect when used with 80 – 90 mg oral morphine[22] .

3.4.2.2 Pre-procedural sedation & analgesia

Oral ketamine prior to colonoscopy, wound management[23,24,25] and dental procedures [26, 27, 28] provides a more pleasant induction of sedation and analgesia than IM or IV use.

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20 Kannan TR, Saxona A, Bhatnager S, Barry A. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. *J Pain Symptom Management* (2002) **23**(1):60–65

21 Enarson MC, Hays H, Woodroffe MA. Clinical experience with oral ketamine. *J Pain Symptom Manage* (1999) **17**(5):384-86

22 Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL. Oral ketamine and transdermal nitroglycerine as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthiol* (1999) **90**(6):1528-3

23 Younge PA, Kendall JM. Sedation for children requiring wound repair: a randomized controlled double blind comparison of oral midazolam and oral ketamine. *Emerg Med J* (2001) **8**(1):30-3

24 Humphries Y, Melson M, Gore D. Superiority of oral ketamine as an analgesic and sedative for wound care procedures in the pediatric patient with burns. *J Burn Care Rehab* (1997) **18**(1 Pt 1):34-6

25 Hollman GH, Perloff WH. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Paed Emerg Care* (1995) **11**(6):399

26 Damle SG, Gandhi M, Laheri V. Comparison of oral ketamine and oral midazolam as sedative agents in pediatric dentistry. *J Ind Soc Pedodont Prevent Dentistry* (2008) **26**(3):97-101

27 Bui T, Redden RJ, Murphy S. A comparison study between ketamine and ketamine-promethazine combination for oral sedation in pediatric dental patients. *Anesthesia Progr* (2002) **49**(1):14-8

28 Roelofse JA, Joubert JJ, Swart LC, Stander I, Roelofse PG, An evaluation of the effect of oral ketamine and standard oral premedication in the sedation of pediatric dental patients. *J Dental Assoc S Afr* (1996) **51**(4):197-201

Oral ketamine 10 mg/kg provided effective sedation and analgesia in 30 young children undergoing wound repair in a prospective, double-blind, placebo-controlled trial[29]. The injection was diluted in wild cherry flavoured syrup, and the placebo was prepared with tonic water to mimic the bitter taste of the ketamine. The ketamine group had a greater tolerance to both lidocaine injection ($p < 0.001$) and suturing ($p = 0.009$) compared with the placebo group. The ketamine group demonstrated greater sedation ($p = 0.012$) without significant respiratory or circulatory adverse events.

*I*mproved analgesia and sedation have been reported with oral ketamine administered as a suspension compared with paracetamol/codeine/diphenhydramine for burns management in 19 children[30]. Ketamine 10 mg / kg body weight given 20 minutes before starting wound care procedures demonstrated >400 % reduction in pain ($p < 0.05$) and >360 % improvement in sedation ($p < 0.5$). Side effects were less than seen with IV administration and did not include respiratory depression seen with narcotics.

3.4.2.3 Premedication prior to anaesthesia

6 mg/kg ketamine administered in sour cherry juice reduced the incidence of emergence agitation in children following adenotonsillectomy from 56 % to 18 % ($p = 0.001$)[31]. There was no evidence of delayed recovery. Although a dose of 3 mg/kg has been found to be effective and associated with decreased incidence of side effects[32], 6 mg/kg produced more predictable sedation within 20 - 25 minutes[33].

In 80 children undergoing elective surgery, although recovery from anaesthesia was longer than for other groups, 8 mg/kg, ketamine was found to be an effective oral premedication[34].

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29 Qureshi FA, Mellis PT, McFadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Paed Emerg Care* (1995) **11**(2):93-97

30 Humphries Y, Melson M, Gore D. Superiority of oral ketamine as an analgesic and sedative for wound care procedures in the pediatric patient with burns. *J Burn Care Rehab* (1997) 18:34 - 6

31 Kararmaz A, Kaya S, Turhanoglu S, Ozylimaz MA. Oral ketamine can prevent emergence agitation in children after desflurane anaethesia. *Paed Anaesth* (2004) **14**(6):477 - 82

32 Sekerci C, Donmez A, Ates Y, Okten F. Oral ketamine premedication in children (placebo controlled double-blind study). *Eur J Anesthesiol* (1996) **13**(6):606-11

33 Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanaesthetic medication in children. *Anesthesiology* (1992) **76**(1):28-33

34 Terhanoglu S, Kararmaz A, Ozyilmaz MA, Kaya S, Tok D. Effects of different doses of oral ketamine for premedication of children. *Eur J Anaesthesiol* (2003) **20**(1):56-60

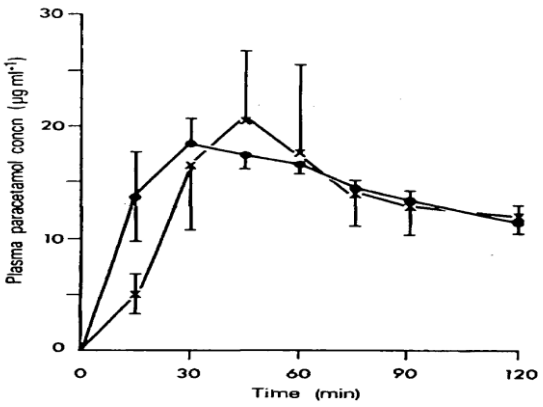
3.5 PK considerations

3.5.1 Effect of ketamine on gastric emptying

When considering the potential for increasing the rate of absorption of a drug it is important to consider the effect of that drug per se on gastric emptying. Given the pharmacological action of ketamine, the possibility that ketamine would slow gastric emptying and hence slow the rate of absorption was considered quite high. However in relation to regular oral administration of the drug, there is no evidence that there will be delayed gastric emptying that might compromise the absorption of subsequent doses once steady state plasma levels are achieved.

IM ketamine at analgesic doses of 0.5 mg/kg has been shown to have no effect on gastric emptying based on the absorption of oral paracetamol in fasted healthy adults shown in Figure 2 [35]. Paracetamol was administered dissolved in 200 mL orange juice with plasma samples taken after 15, 30, 45, 60, 75, 90 and 120 minutes. For placebo, mean C_{max} was 20.3 ± 2.3 mcg/mL with a mean T_{max} of 36 ± 7.6 minutes, compared with mean C_{max} of 23.8 ± 5.3 mcg/mL and a mean T_{max} of 63 ± 16 minutes following IM ketamine.

Figure 2 Effect of 0.5 mg/kg ketamine IM (✕) and placebo (●) on paracetamol absorption profiles in five fasted healthy adults



Although these mean values appear different, the authors noted that paracetamol absorption profiles were almost identical for four of the five subjects in the ketamine and control studies, with one subject showing delayed absorption possibly attributable to anxiety. Based on these results, they concluded that, compared with narcotic analgesics which significantly depress gastro-intestinal activity, ketamine did not delay gastric emptying.

[35] Grant IS, Nimmo WS, Clements JA. Lack of ketamine analgesia on gastric emptying in man. *Br J Anaesth* (1981) **53**: 1321 -1323

Of interest was that the observed T_{max} results of 36 and 63 minutes for paracetamol in solution in the orange juice were much slower than for paracetamol solutions and Surge Dose® tablets in the Imaginot studies where T_{max} values were in the range 9 – 20 minutes[36]. However the slower absorption of paracetamol from orange juice in this study is consistent with the effects of the sugar and fibre content of the fruit juice which has been reported to delay gastric emptying and hence delay absorption.

3.5.2 Variability

As shown in Table 1, PK values for individual subjects show a high degree of variability in C_{max} and T_{max} (time to C_{max}) after oral administration of a ketamine solution.

Table 1 PK values for six fasted healthy adults following oral administration of 0.5 mg/kg ketamine (Grant et al 1981)

	Ketamine		Norketamine		
Subject	Peak concn ($ng\,ml^{-1}$)	Peak time (min)	Peak concn ($ng\,ml^{-1}$)	Peak time (min)	Bioavailability (%)
DB	30	45	190	60	14.5
JC	35	30	220	60	16.3
FH	15	45	65	120	—
DL	35	20	390	45	11.2
WM	80	20	165	30	—
WN	70	20	160	45	24.5

Variable T_{max} values for ketamine were observed between 20 and 45 minutes following oral administration and C_{max} values were quite variable ranging from 15 to 80 ng/mL. T_{max} values for the metabolite norketamine were correspondingly longer ranging from 30 – 120 minutes, again with variable C_{max} values ranging from 65 to 390 ng/mL. In general, slower absorption was associated with lower C_{max} values, and faster absorption with higher C_{max} values.

Given that the drug is already in solution when administered, the variability in absorption profiles must be attributable to variable gastric emptying of the 50 mL solution, which can get trapped within the mucosal folds in the stomach until emptied during a high activity phase of the MMC. Such increased variability with low volumes of solution was observed in the pilot PK studies on paracetamol[37]. Using volumes of 100 - 250 mL, T_{max} values in

[36] Imaginot Pty Ltd. CR 01-01-01 Overview of human pharmacokinetic trials to identify factors for fast gastric emptying and fast absorption of paracetamol (Protocol PAH 136.02) May 2007

[37] Imaginot Pty Ltd CR 01-01-01 Overview of human pharmacokinetic trials to identify factors for fast gastric emptying and fast absorption of paracetamol (Protocol PAH 136.02) May 2007

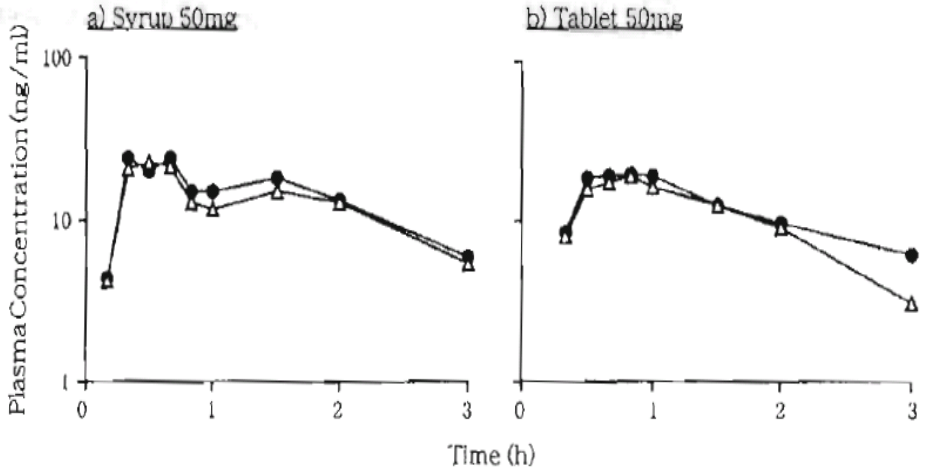
the range 9 – 20 minutes were achieved for paracetamol solutions with similar T_{max} values achieved for Surge Dose® formulations.

Based on these observations swallowing a Surge Dose® ketamine tablet with 100 – 200 mL water should be advantageous in providing a bolus of water into which the drug can actively dissolve before emptying into the small intestine whence absorption will occur.

3.5.3 Formulation effects

Absorption of ketamine appears to be slower from conventional tablets than from a syrup based on published plasma concentration – time profiles shown in Figure 3[38].

Figure 3 PK profiles for oral administration of 50 mg ketamine as a syrup and a tablet to a healthy volunteer (n=1) showing plasma levels of R-ketamine (●) and S-ketamine (△)



Ketamine was absorbed more slowly from the tablets with T_{max} around 50 minutes for both racemates compared with 20 and 30 minutes respectively for the R- and S-racemates for the syrup. C_{max} and area under the curve over the first 3 hours post-dosing were slightly lower with the tablets than the syrup. C_{max} values were 20.0 and 19.2 ng/mL for the tablets and 23.7 and 22.3 ng/mL for the syrup.

This slower absorption suggests that in vivo dissolution is rate limiting for the absorption of ketamine from tablet formulations compared with the syrup where the drug is already in solution. Faster absorption results in higher C_{max} values.

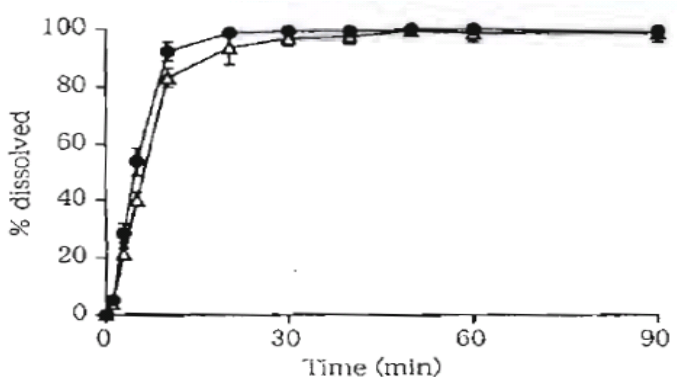
Of interest is the biphasic shape of the absorption profile for the syrup suggesting the release of an initial bolus to drive absorption followed by slower release of the remainder

[38] Yanagihara Y, Ohtani M, Matsumoto M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, Aoyama T, Yamamura Y, Iga T. Preparation of ketamine tablets for treatment of patients with neuropathic pain. *Yakugaku Zasshi* (1999) **119**(12):980 - 987

of the dose leading to a second absorption phase after about an hour which would be consistent with complete gastric emptying in Phase 3 of the MMC.

No such biphasic absorption is evident for the tablet for which dissolution profiles are shown in Figure 4, achieving 50 % dissolution in 6 minutes and 90 % dissolution in 16 minutes under low stirring conditions at approximately neutral pH. While relatively fast, this is slower than Surge Dose® tablets which exceed 70 % dissolution in the first 3 minutes, with a target of greater than 90 % dissolution in 3 minutes for optimised formulations.

Figure 4 Dissolution profiles for ketamine tablets in a dissolution medium pH 6.8 with paddles rotating at 25 rpm (△) and 40 rpm (●)



A more recent paper reports the development of a stable ketamine 25 mg gelatine based lozenge for oral administration that can be swallowed or allowed to dissolve slowly in the mouth for sublingual administration[39]. PK profiles for IM administration and for the lozenge swallowed and dissolved in the mouth are shown in Figure 5 with PK parameters summarized in Table 2. This study found slower absorption from a swallowed lozenge with a median T_{max} of 2 (range 1.2 – 2.5) hours compared with only 30 (range 18 – 48) minutes when the lozenge was dissolved in the mouth allowing the drug to be absorbed sublingually. In both cases T_{max} and C_{max} values showed high variability which was greater for the swallowed lozenge consistent with variable in vivo dissolution and gastric emptying.

[39] Chong C, Achug SA, Page-Sharp M, Jenkins B, Ilett KF. Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Invest* (2009) **29**(5):317-24

Figure 5

PK profiles for ketamine and norketamine in patients with chronic neuropathic pain

(a) 10 mg IV (n = 6)

(b) 25 mg swallowed (n = 6) and

(c) 25 mg sublingually (n = 5)

(Chong et al 2009)

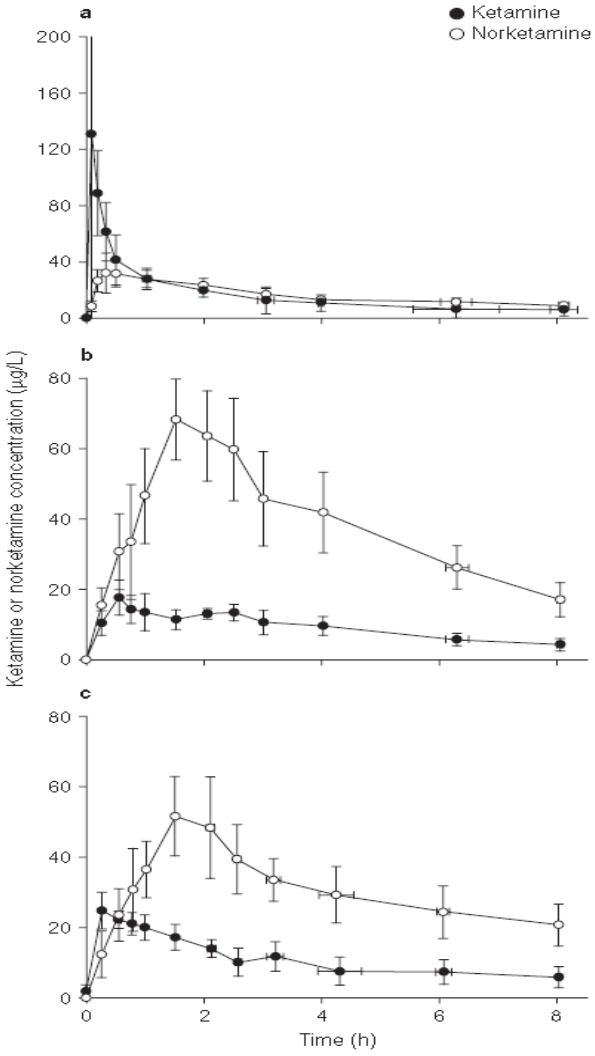


Table 2 Median PK parameters for ketamine and norketamine in patients with chronic neuropathic pain (a) 10 mg IV (n = 6) (b) 25 mg swallowed (n = 6) and (c) 25 mg sublingually (n = 5) (Chong et al 2009)

Parameter	Ketamine			Norketamine		
	intravenous	sublingual	oral	intravenous	sublingual	oral
$t_{1/2}$ (h)	5.2 (3.4–6.4)	5.1 (4.1–8.2)	5.6 (3.6–7.1)	5.5 (4.3–7.9)	6.4 (5.1–7.1)	3.9 (3.1–5.8)
V_z (L/kg)	5 (4–6)	19.7 (9.9–26.4)	24.5 (19–26)	NC	NC	NC
CL (L/h/kg)	0.9 (0.7–0.9)	4 (1–4.25)	3 (3–5)	NC	NC	NC
C_{max} (µg/L)	202 (123–344)[a]	30 (24–32)	21 (12–35)	26 (20–48)	74 (41–85)	86 (69–107)
t_{max} (h)	NA	0.5 (0.3–0.8)	2 (1.2–2.5)	0.33 (0.33–0.46)	1.8 (1.5–2)	1.5 (0.9–2.3)
AUC_8/dose (µg • h/L/mg)	13.3 (11–16)	4.2 (2.6–6.5)	2.5 (2.1–3.7)	11.2 (9.4–14)	8.8 (6.7–12.9)	12.7 (8.6–16)
Bioavailability (%)[b]	NA	24 (19–49)	24 (17–27)	NA	NA	NA

a Estimated C_0.

b From AUC_8 data.

AUC_8=area under the plasma concentration-time curve from baseline to 8 hours; **C_0**=extrapolated zero time concentration-axis intercept; **CL**=clearance; **C_{max}**=maximum plasma concentration; **NA**=not applicable; **NC**=not calculated; **$t_{1/2}$**=half-life; **t_{max}**=time to reach C_{max}; **V_z**=volume of distribution in the elimination phase.

No dissolution data are provided for the gelatine based lozenge but it would be expected to be quite slow as it is not a traditional tablet formulation containing water uptake agents and disintegrants such as that reported by Yanagihara et al (1999)[40]. The slower dissolution of this type of formulation in vivo is consistent with the reported slower absorption of the ketamine from this dosage form.

In contrast, the lozenge when dissolved in the mouth for 10 minutes will produce a solution of ketamine, and while the faster absorption may be attributable in part to sublingual absorption, it may also be attributable to faster absorption of this drug from solution as the median T_{max} value is consistent with those reported for ketamine syrup.

3.6 PK-PD correlation

3.6.1 Analgesia

The PK and analgesic effects of ketamine in fasted healthy adults have been reported at different sub-anaesthetic doses following administration by IV bolus, IM injection and as an oral solution administered with 50 mL orange juice [41, 42, 43.] Analgesia was assessed by measuring the time in seconds to reach an intolerable pain threshold using the sub-maximal effort tourniquet test before drug administration, with drug and with placebo.

In the study comparing IM and oral administration of 0.5 mg/kg, all 6 subjects remained conscious and oriented but some light headedness was reported 20 – 45 minutes after IM injection. The periods of pain free ischaemic exercise at 15 and 30 minutes after IM administration and at 30 minutes after oral dosing are shown in Table 3 indicating a slower onset of action of 30 minutes for the oral dose compared with 15 minutes for IM.

These results indicate that pain thresholds were increased for both routes of administration, at 15 and 30 minutes after IM administration and at 30 minutes after oral administration. However, the authors concluded that 0.5 mg/kg orally was insufficient to produce acceptable consistent levels of analgesia.

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[40] Yanagihara Y, Ohtani M, Matsumoto M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, Aoyama T, Yamamura Y, Iga T. Preparation of ketamine tablets for treatment of patients with neuropathic pain. *Yakugaku Zasshi* (1999) **119**(12):980 - 987

[41] Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* (1981) **53**:27 - 30

[42] Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of IM and oral ketamine. *Br J Anaesth* (1981) **53**:805-810

[43] Grant IS, Nimmo WS, Clements JA. Bioavailability, pharmacokinetics and analgesic activity of ketamine in humans. *J Pharm Sci* (1982) **71**:539-42

Table 3 ***Times (seconds) to reach intolerable pain following IM and oral administration of 0.5 mg/kg to six fasted healthy adults († not statistically different from control; ** significantly greater than control P<0.05) (Grant et al 1981)***

Study	Before drug administration	Time after drug administration (min)				
		0	15	30	45	60
Control	88.7±2.7	98.7±2.9	89.2±3.5	90.0±3.1	87.0±3.2	88.8±2.8
Oral ketamine 0.5 mg kg^{-1}	99.0±5.9†	102.7±5.7	103.0±4.8	108.8±4.8**	106.0±7.6	101.0±7.9
I.m. ketamine 0.5 mg kg^{-1}	98.2±3.6†	101.3±5.9	122.2±7.9**	118.7±7.5**	104.3±6.2	103.0±7.8

Mean plasma concentration – time profiles for the two routes of administration for the parent drug and its major active metabolite norketamine are shown in Figures 6 and 7. These show a higher mean C_{max} value of around 200 ng/mL (100 – 425 ng/mL) for IM ketamine compared with only 15 – 80 ng/mL for oral administration. In contrast, oral administration resulted in much higher levels of the active metabolite norketamine, ranging from 65 – 390 ng/mL, compared with a mean level of around 80 ng/mL for IM injection as a result of greater hepatic first pass metabolism with oral administration.

Figure 6 ***Mean plasma ketamine (×) and norketamine (●) levels following IM administration of 0.5 mg/kg to six fasted healthy adults (Grant et al 1981)***

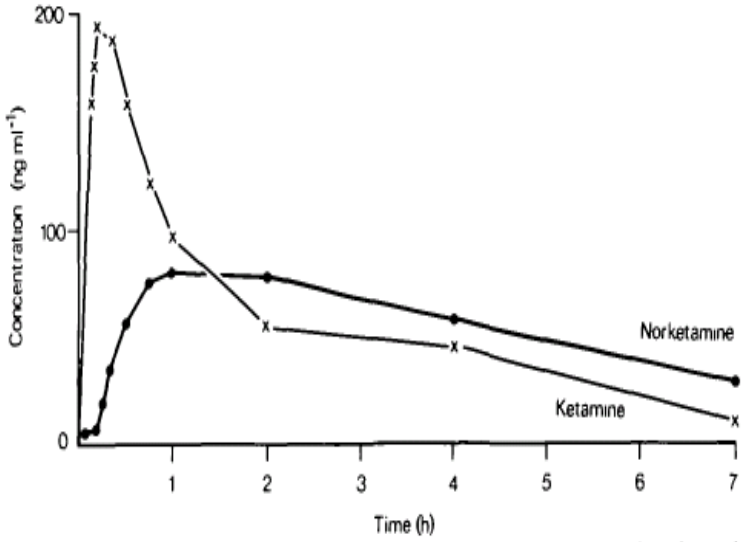
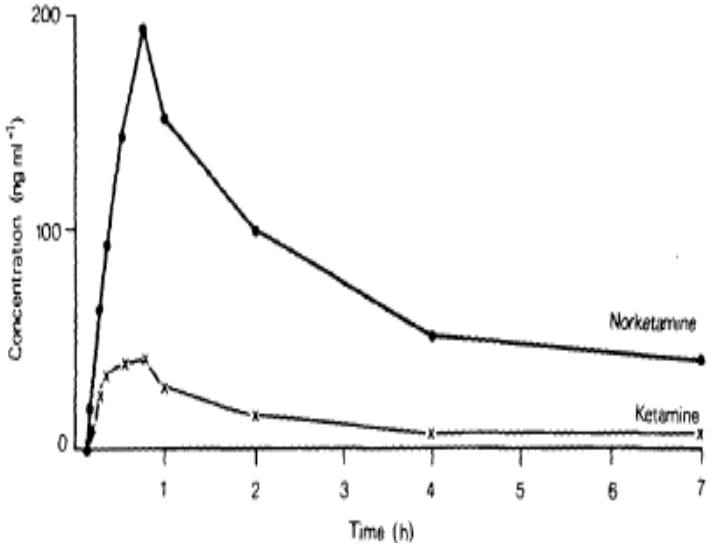


Figure 7 Mean plasma ketamine (×) and norketamine (●) levels following oral administration of 0.5 mg/kg to six fasted healthy adults showing the effects on first-pass hepatic metabolism to norketamine (Grant et al 1981)



These results suggest that the higher levels of the active metabolite norketamine resulting from first-pass hepatic metabolism after oral dosing contribute to the analgesia observed at much lower levels of ketamine compared with IM administration. A potential advantage of oral administration is that these lower peak plasma levels may avoid some of the less desirable side effects seen with IM and IV administration.

3.6.2 Sedation

Oral ketamine has been evaluated as a premedication in children at higher doses than used for analgesia in a number of studies. Doses were administered in low volumes 10 – 20 mL prior to anaesthesia. These studies showed rapid onset of action observed within about 10 minutes, and maximum sedation in around 20 minutes.

In a prospective study in 35 paediatric oncology patients aged from 14 months to 17 years, sedation was observed within 45 minutes in 87 % of subjects[44]. Recovery was uneventful within 2 hours with 91 % of subjects showing no signs of emergence phenomena frequently seen with injectable use. The drug was administered at a dose of 10 mg/kg diluting the injection in 0.3 mL/kg of a beverage of choice to mask the bitter taste of the injection which was a problem for some patients.

[44] Tobias JD, Phipps S, Smith B, Mulhern RK. Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. *Pediatrics* (1992) **90**(4): 537 - 541

In another prospective, randomized, double blind study, 80 children undergoing elective surgery received 10 mL orally containing 4, 6 or 8 mg/kg mixed with sour cherry juice [45]. The group receiving 8 mg/kg was significantly calmer with an onset time of sedation of 9.5 ± 1.9 minutes and adequate sedation in 80 % of patients, compared with the groups receiving lower doses. This dose is recommended for premedication although recovery from propofol anaesthesia was longer but still within 2 hours.

Compared with 3 mg/mL, an oral dose of 6 mg/mL was effective and well accepted as a premedication achieving uniform sedation in 20 – 25 minutes post dosing [46]. The drug was administered as the injection mixed with 0.2 mL/kg of a cola flavoured soft drink, the taste of which was still unacceptable to 11 % of the 45 children in the study. For the 3 mg/mL dose, 73 % of subjects were sedated with a mean onset of sedation of 12.5 ± 1.3 minutes and maximum sedation at 19.6 ± 3.6 minutes. 100 % sedation was achieved with 6 mg/mL where the mean onset of sedation was 11.2 ± 2.4 minutes and maximum sedation occurred at 19.6 ± 4.6 minutes.

3.6.3 Therapeutic plasma levels

Plasma concentrations of 800 – 4,000 ng/mL are associated with hypnosis and amnesia following surgery, with awakening at levels below 500 ng/mL and elevated pain threshold levels around 100 ng/mL[47].

Analgesia is evident at much lower plasma concentrations than those producing anaesthesia where the lowest levels of ketamine associated with return of consciousness are around 600 – 700 ng/mL. Following IV administration of 0.125 and 0.25 mg/kg, analgesia was reported with ketamine plasma levels above 100 ng/mL[48], and when administered IM at 0.5 mg/kg, above 150 ng/mL [49]. However when 0.5 mg/kg was administered orally, analgesia was associated with ketamine plasma levels above only 40 ng/mL albeit associated with much higher levels of the active metabolite norketamine than seen when the drug is used parenterally.

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[45] Turhanoglu S, Kararmaz A, Ozyilmaz MA, Kaya S, Tok D. Effects of different doses of oral ketamine for premedication of children. *Eur J Anaethesiol* (2003) **20**: 56 – 60

[46] Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral preanaesthetic medication in children. *Anesthesiol* (1992) **76**:28 - 33

[47] Anderson BJ & Palmer GM. Recent developments in the pharmacological management of pain in children. Curr Opin Anaesthesiol (2006) 19:285 - 92

[48] Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* (1981) **53**(1):27-30

[49] Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of IM and oral ketamine. *Br J Anaesth* (1981) **53**(8):805-810

Oral administration of solutions produces T_{max} values of 20 – 45 minutes, so if similarly fast absorption can be achieved with a tablet formulation, similarly fast onset of action should be achievable. pH control and activated dissolution provided by the Surge Dose® technology provides tablets where in vivo dissolution is not rate limiting as seen with conventional passively dissolving tablets.

4 Suitability of ketamine as a Surge Dose® candidate

Based on the following considerations, ketamine appears to be a suitable candidate for presentation as a Surge Dose® tablet with associated faster in vitro and in vivo dissolution and subsequent faster absorption and onset of action than would be obtained with a conventional tablet formulation.

4.1 Solubility

Ketamine has high solubility and a Surge Dose® ketamine formulation would be designed to maximise dissolution of the drug in the coadministered water and any gastric contents:

- Doses up to 500 mg should easily dissolve in the volumes of fluid available in vivo and in any co-administered water with which the drug is swallowed.
- As a base, solubility will be greatest under acidic gastric conditions reducing as the pH increases. If the drug has not been completely dissolved in the stomach, then solubility will be reduced with slower dissolution in the more alkaline intestinal conditions which will impact absorption.
- If the drug is totally dissolved in acidic conditions, the possibility of re-precipitation as dissolved drug reaches the higher pH conditions in the small intestine needs to be considered.

4.2 Intestinal Permeability

Ketamine has high passive intestinal permeability and so high concentrations of dissolved drug obtained with a Surge Dose® formulation will readily drive absorption:

- Using quantitative structure PK relationships (QSAR), the bioavailability of ketamine has been estimated as 53 % [50] and 67 %[51], both higher than the actual bioavailability around 20 % which is low as a result of first-pass hepatic metabolism rather than limited intestinal permeability.

[50] Turner JV, Maddalena DJ, Agatonovic-Kustrin S. Bioavailability prediction based on molecular structure for a diverse series of drugs. *Pharm Res* (2004) **21**(1):68 – 82

[51] Turner JV, Glass BD, Agatonovic-Kustrin S. Prediction of drug bioavailability based on molecular structure. *Anal Chim Act* (2003) **485**:89 - 102

- As compounds with absorptive permeability values above 100 nm/s are classified in the BCS as highly permeability, ketamine with a value of 748 nm/s meets the criterion for a high permeability drug. When considered with the BCS classification of highly soluble based on the D_0 value of 0.008, ketamine is a BCS class 1 drug which would qualify for a waiver on bioavailability or bioequivalence studies relative to oral formulations if such were already approved by the FDA [52].

- The Efflux Ratio (ER) for ketamine is 0.9 based on its absorptive permeability of 748 nm/s and a secretory permeability of 695 nm/s. This is below the limit of 1.5 above which some extent of P-gp (P-glycoprotein) mediated efflux occurs which would reduce the bioavailability. This indicates that ketamine is not a substrate for P-gp and so this is not contributing to the observed lower bioavailability [53].

- Another predictor of bioavailability considering the ionic nature of a drug molecule is based on the observed higher bioavailability of acidic molecules compared with bases, with neutral molecules being intermediate[54]. This is important as both absorption and hepatic metabolism are mediated through the unionised form. This parameter is △logD (the difference between the distribution coefficients at pH 6.5 and at pH 7.4) being negative for bases and positive for acidic drugs. The △logD value for the base ketamine is - 0.69. The optimum log $D_{6.5}$ for the overall processes of absorption and first-pass effect is 0.7, and for bioavailability alone - 0.3. Ketamine has a log $D_{6.5}$ of - 0.69 which is within the range of - 2.0 to 3.0 observed for highly bioavailable drugs.

- Another key factor affecting intestinal permeability is the molecular flexibility for which the number of rotatable bonds is a good predictor [55]. These are defined as any single bond, not in a ring, bound to a non-terminal heavy (non-hydrogen) atom, excluding any amide C-N bonds because of their high rotational energy. Compounds with 10 or less rotatable bonds have high bioavailability. As seen in Figure 1, ketamine has 2 rotatable bonds around the chiral centre which is predictive of high intestinal permeability and good bioavailability

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[52] US DHHS FDA CDER (2000) Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a Biopharmaceutics Classification System.

[53] Varma MVS, Sateesh K, Panchagnula R. Functional role of P-glycoprotein in limiting intestinal absorption of drugs: contribution of passive permeability to P-glycoprotein mediated efflux transport. *Mol Pharm* (2005) **2**(1):12 - 21

[54] Yoshida F, Topliss JG. QSAR model for drug human oral bioavailability. *J Med Chem* (2000) **43**:2575 - 2585

[55] Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem* (2002) **45**: 2615 - 2623

Other factors that are predictive of high intestinal permeability for ketamine are [56]:

- MW less than 500 – ketamine has a MW of 237.7 and the HCl salt 274.2
- a total polar surface area (TPSA) equal to or less than 140 $Å^2$ – ketamine has a value of 29.1
- calculated octanol-water coefficient (C log P) less than 5 – ketamine has a value of 2.93

4.3 PK-PD Correlation

Based on the PK and PD data published on the oral administration of ketamine solutions, there is good correlation with fast absorption and fast onset of action making ketamine a good Surge Dose® candidate.

Using ketamine injection administered orally in a flavoured vehicle, onset of sedation is reported at around 10 – 15 minutes compared to around 30 minutes for onset of analgesia.

Although T_{max} values for ketamine solution administered orally are around 1 hour, therapeutic levels associated with analgesia of 40 ng/mL are reached within 15-30 minutes. The faster onset of sedative activity may be associated with lower plasma levels as the drug rapidly passes across the blood-brain barrier to exert a central effect in contrast to peripheral analgesic effects.

A significant advantage of this good correlation is that PK-PD studies can be designed to incorporate non-invasive PD measures for sedation and/or analgesia in healthy volunteers.

5 Development of Surge Dose® ketamine

5.1 IP considerations

Imaginot has a patent portfolio of three patent families covering its Surge Dose® technology which exemplify a wide range of actives based on four general chemical classes of molecules classified as basic, amphoteric, acidic and unionised:

i. PCT/AU 2006/001798 covers basic, amphoteric, acidic and unionised therapeutic agents claiming priority from three Australian provisionals, one filed on 28 November 2004 and two on 13 May 2005. This has been filed in US, Canada, Europe, India, Japan, Australia and during examination has been restricted to

[56] Varma MVS, Sateesh K, Panchagnula R. Functional role of P-glycoprotein in limiting intestinal absorption of drugs: contribution of passive permeability to P-glycoprotein mediated efflux transport. *Mol Pharm* (2005) **2**(1):12 - 21

acidic and unionised drugs. This patent has been granted in Australia and is under examination elsewhere,

ii. PCT/AU 2005/00759 covers basic and amphoteric actives claiming priority from 28 May 2004. Filed in US, Canada, Europe, India, Japan, Australia, this patent has been granted in Canada and Australia and is under examination elsewhere.

iii. PCT/AU 2005/00758 covers paracetamol claiming priority from 28 May 2004. This patent has been granted in US and Canada and has been assigned to another company in Europe, India, Japan and Australia.

While not specifically named or exemplified in the Imaginot patents, ketamine is a basic molecule and would be covered by the second patent family.

5.2 Dose considerations

Although no ketamine solid dosage form appears yet to have been registered, a range of tablets containing 25, 50 and 100 mg ketamine would provide reasonable flexibility to administer oral doses for both adults and children starting at around 0.5 mg/kg.

Ideally, the tablets should be given with a volume of co-administered water around 150 – 200 mL in which the drug will dissolve in vivo, so that the resultant solution flows through and out of the stomach independent of gastric motility and the MMC to achieve early absorption from the small intestine.

5.3 Formulation considerations

An optimised Surge Dose® ketamine tablet formulation containing the equivalent of 40 mg ketamine base has been developed using customised levels of pH modulating agents (pHMA) and water uptake agents to maximise in vivo dissolution rates compared with conventional tablet formulations[57].

Surge Dose® ketamine tablets each weighing 250 mg demonstrated ultra-rapid in vitro dissolution in a medium containing 3 mmoles HCl at 37 ºC under low stirring conditions exceeding 90 % dissolution in 3 minutes. This is faster than the dissolution of an experimental tablet formulation reported by Yanagihara et al (1999) which achieved 50 % dissolution in 6 minutes and 90 % dissolution in 16 minutes under low stirring conditions in pH 6.8 buffer which demonstrated dissolution rate limited absorption compared to ketamine administered in solution.

[57] IM 03-16-02 Surge Dose® technology transfer for ketamine hydrochloride. Imaginot Pty Ltd. March 2008

5.4 Stability considerations

Ketamine HCl shows good chemical stability with aqueous injectable formulations registered with a shelf life of 2 years without the need for refrigerated storage

Tablets can be film coated but as they contain moisture sensitive pHMA, controlled low relative humidity conditions are required for manufacture and unit dose packaging is required for maximum stability. The optimised Surge Dose® ketamine tablets showed satisfactory physical and chemical stability consistent reports on other solid dosage forms:

- A 150 mg tablet produced by wet granulation containing 50 mg ketamine showed good stability after 12 weeks at 25 °C and 75 % relative humidity[58]. These tablets were suitable for commercial manufacture and film coating with the following values for hardness (7.2 kg/cm^2), friability (0.4 %), content uniformity, weight variation and disintegration time (172.6 seconds).
- A gelatine based lozenge formed in a suppository mould and rolled in lactose each containing 25 mg ketamine hydrochloride has also been shown to have satisfactory physical and chemical stability after storage for 14 weeks at 2 – 8 ºC and 25 ºC[59].

5.5 Clinical considerations

A cost-effective PK-PD study design in healthy volunteers would include non-invasive measures for sedation and/or analgesia.

An optimised Surge Dose® ketamine tablet should achieve an absorption profile closer to a solution product than a conventional tablet formulation with T_{max} values less than 30 minutes and a correspondingly fast onset of action, in the region of 10-15 minutes for sedation and 20-30 minutes for analgesia.

Since the adverse events associated with ketamine are dose related and dose limiting, more consistent absorption from an optimised Surge Dose® ketamine tablet should allow the use of lower oral doses which will minimise the potential for side effects without compromising efficacy.

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[58] Yanagihara Y, Ohtani M, Matsumoto M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, Aoyama T, Yamamura Y, Iga T. Preparation of ketamine tablets for treatment of patients with neuropathic pain. *Yakugaku Zasshi* (1999) **119**(12):980 - 987

[59] Chong C, Achug SA, Page-Sharp M, Jenkins B, Ilett KF. Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Invest* (2009) **29**(5):317 - 24

6 Conclusion

Based on this review of its physicochemical, PK and PD properties following oral administration, ketamine HCl appears to be a suitable candidate for application of the Surge Dose® ultra-rapid dissolution technology:

- **High aqueous solubility** – the HCl has a solubility of 250 mg/mL such that doses of up to 500 mg should readily dissolve in around 2 mL water
- **High permeability** - readily absorbed from the small intestine with rapid distributed throughout the body
- **Good PK-PD correlation** – fast absorption and onset of action following oral administration of solutions produces T_{max} values of 20 – 45 minutes. If the time for onset of analgesia is similar to sedation onset following oral administration of a solution, then onset of analgesia could be expected within 10 minutes.

An optimised Surge Dose® ketamine tablet should achieve absorption profiles closer to those seen with a solution compared with conventional tablet formulations with T_{max} values less than 30 minutes and a correspondingly fast onset of action, in the region of 10-15 minutes for sedation and 20-30 minutes for analgesia.

Ketamine appears to have good chemical stability in solution and in tablet formulations, such that it should be possible to develop a robust, stable tablet formulation that is suitable for commercial manufacture.

A Surge Dose® tablet formulation will be more convenient and avoid palatability issues as well as achieving fast absorption similar to the administration of a solution, and offering the potential for reduced variable absorption. More consistent absorption from an optimised Surge Dose® ketamine tablet should also allow the use of lower oral doses which will minimise the potential for side effects without compromising efficacy.