Comments on 'Ketamine hydrochloride – an adjunct for analgesia in dogs with burn wounds'

In an article entitled 'Ketamine hydrochloride – an adjunct for analgesia in dogs with burn wounds' (Joubert K, *Journal of the South African Veterinary Association* (1998) 69(3): 95–97), the author advocates in his conclusions the clinical use of ketamine with opioids and sedatives in complex management of severe pain in the dog. Although he gives a good

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theoretical justification for the case of analgesic use of ketamine, his clinical evidence does not provide enough data to support this conclusion, as:

1. Only 2 cases are presented and no control group without the use of ketamine is provided.
2. Ketamine was used only late in the course of pain management in both dogs. Indeed, the expected clinical effect of any analgesic drug should theoretically be better when the drug is given as soon as possible after the onset of pain.
3. The author does not specify his criteria for evaluation of clinical analgesia in the dogs. He states in conclusion that 'the clinical endpoint of pain management should allow procedures to be performed on the patient with minimal discomfort, and food and water intake should remain acceptable.' Nevertheless, it is stated that Dog no. 1 started to be interested in food only 4 days after the beginning of the ketamine administration. Pain relief was apparently incomplete in Dog no. 2 for days after the beginning of administration of ketamine. Additionally, the dog was showing signs of discomfort, vomition and mental depression, which might also be indicative of insufficient pain-relief.

I would suggest that the author tests his working hypothesis in a larger number of dogs using early administration of ketamine together with selected complementary analgesic drugs (among opioids, morphine would appear to be the drug of choice against buprenorphine in the case of severe pain). The suggested use of hypnotic drugs such as thiopentone or propofol together with ketamine would not be advisable for the purpose of 'total control of pain'.

In order to substantiate the working hypothesis, it would be further necessary to provide data concerning clinical performance of dogs treated with other analgesic drugs only (*i.e.* in a control group). Finally, the criteria for evaluation of pain and discomfort, as well as the incidence of possible side-effects of ketamine, should be given in detail.

In conclusion, until reliable clinical data are available, ketamine should not be claimed to be an effective and safe analgesic in critically-ill canine patients suffering from severe pain.

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In reply to Dr J Still

1. *Only 2 cases presented and no control group ....*

The intention of this article was to report on the clinical usage of ketamine as an analgesic. It was not designed as a clinical trial and hence no control groups were used. The aim of this article was to introduce the concepts of peripheral and central hypersensitisation, explain part of the physiological concept behind it and to give a possible therapeutic answer. The balance of evidence in human patients would indicate that ketamine is able to control central hypersensitivity pain.

2. *Ketamine was only used late in the course of pain ....*

It is largely true to say that if analgesic agents are started early in the course of pain a better effect should be obtained. In actual fact if one could start the analgesic before the insult, the analgesia should be greatly improved. On this basis, the concept of pre-emptive analgesia was born. Pre-emptive analgesia has produced inconsistent results for a number of reasons[11]. The use of NMDA receptor antagonists (ketamine) for the prevention of post-operative pain on a pre-emptive basis is currently undergoing research[7,8,11,19].

Both patients started on an opioid-based analgesic protocol. Patient 1 started on morphine (day 1) and then continued with buprenorphine (days 2, 3, 4) while patient 2 received buprenorphine only. Despite the opioid-based analgesic protocol, these patients presented with severe, intractable pain (patient 1, day 4; patient 2, day 2). This pain developed as a consequence of central hypersensitivity. Central hypersensitivity is mediated through the opening of NMDA channels and other glutamate-based receptor channels from the influence of substance P and glutamate[20]. The opening of these channels is not prevented by opioids[1,12]. Hence opioid analgesic may become ineffective in pain control in patients with central hypersensitivity and furthermore hypersensitivity may occur despite the use of opioids for analgesia[1,12]. In this situation, what pharmacological agents are available to manage this type of pain? Ketamine is a suitable agent owing to the effect it exerts on the NMDA receptor[14].

Pain relief from ketamine was not immediate, as stated, but an immediate improvement in disposition was noted. For reasons beyond my control, the opioids were discontinued in both patients when ketamine was started. I believe that this is not ideal and that by the mechanisms of actions of opioids and ketamine that they are both necessary to manage pain effectively. It is probable that, because ketamine was the only analgesic used, pain was not immediately alleviated and hence the signs possibly indicative of pain were noticed. Ketamine has been shown to increase the quality of pain relief when used in conjunction with opioids[4,15]. This action may be synergistic[4]. There are now efforts to combine the use of opioids and ketamine for pain management in humans[4,18].

The failure of the first patient to show an interest in food may be related to the pharyngostomy tube, which was placed to ensure that 2.5 times the maintenance requirements of energy and protein could be fed, since prehension due to burns sustained on the lips was difficult.

3. *The author does not specify his criteria for the evaluation ....*

The assessment of pain remains one of the most difficult problems in veterinary science. Recent evidence suggests that the use of physiological parameters in the assessment of pain is not accurate[10]. Heart and respiratory rates vary owing to the effects of drugs on the patient and stress levels induced by the hospital and handling[10]. This leaves pain assessment as largely subjective. In these patients, pain was assessed by the ability to handle and perform procedures on the patient along with the behaviours of pain as described by Hansen[9]. A definitive method for the assessment of pain still needs to be outlined for small animal practice.

4. *The suggested use of hypnotic drugs ....*

Propofol was used in the 2nd patient to induce anaesthesia for secondary closure of the burn wound. In this case, propofol was used in combination with morphine for a balanced anaesthetic technique. Patient 1 was anaesthetised with a combination of ketamine and midazolam for the placement of a pharyngostomy tube, also considered a balanced technique.

Benzodiazepines are known to have analgesic properties, over and above the

relief of anxiety, and may offer additional analgesia[3]. Propofol, benzodiazepines and ketamine have been used in human patients for the management of procedural pain related to burns[2,5]. High levels of anxiety and stress have been shown to increase pain scores and relief of the anxiety through pharmacological and non-pharmacological manipulation has been shown to decrease pain scores[6,13]. Although none of these drugs are primary analgesics and they cannot be used for pain management on their own, they form an important part of total pain management. Benzodiazepines, phenothiazines and butyrophenones have been considered as supplemental drugs, should patients be abnormally excited, hyperactive, neurotic or experience psychogenic pain[17]. This may be related to a change in conscious perception of pain and the associated changes of the autonomic nervous system[17]. The roles that anxiety and stress play in animal pain perception is difficult to evaluate.

5. *In order to substantiate the working hypothesis ....*

It is interesting that to date no definitive study of the use of ketamine in human burn patients has been carried out. Recent human medical literature has indicated the use of ketamine for pre-emptive analgesia[7]. A large portion of the working hypothesis of NMDA receptors and their role has been or is in the process of being elucidated[14]. In fact, 7 NMDA receptor blockers are currently undergoing clinical trials in human subjects. (A literature search will reveal a large number of articles in support – Medline lists over 1000 articles). It is hoped with time that a more definitive, controlled study will be carried out in dogs.

'Clinical trials indicate that the practical use of non-competitive NMDA receptor blockers, such as ketamine, dextromethorphan, and memantine will become part of accepted therapeutic regimes in the management of neuropathic pain. They prevent or block central hypersensitive states'[16].

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