Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma: PACKMaN

Justification of intraosseous route of administration for IMP

Prehospital administration of ketamine hydrochloride or morphine sulphate to provide analgesia is a well-established practice in the United Kingdom. Clinical practice guidelines indicate that both drugs may be administered via the intravenous (IV) or intraosseous (IO) routes. However, the investigational medicinal product dossier (IMPD) accompanying this clinical trial does not specify that trial medications can be administered via the IO route. This supplement has been drafted to affirm that administration of trial medications via the IO route is both safe and effective.

In clinical emergencies both fluid and drug administration via the IO route is advocated by the International Liaison Committee on Resuscitation,[1] European Resuscitation Council,[2] Resuscitation Council UK,[3] Royal College of Nurses,[4] Royal College of Emergency Medicine[5] and the Joint Royal Colleges Ambulance Liaison Committee.[6] The IO device (Arrow EZ-IO) used by both participating ambulance services (WMAS, YAS), is CE marked and designed specifically for the purpose of drug administration into the intraosseous circulation. Studies sponsored by Telefex (manufacturer of the Arrow EZ-IO) suggest drugs administered via the IO route reach the heart in less than 3 seconds[7] and that pharmacokinetic properties of drugs administered via the IO route are comparable to those delivered by central venous routes.[8]

We conducted a brief search of the Embase, MEDLINE and Cochrane Libraries to identify studies addressing compatibility of either ketamine hydrochloride or morphine sulphate with IO catheters. We were unable to identify any studies or reports suggesting there may be compatibility concerns. However, our search did identify several studies addressing the clinical efficacy of the IO route during resuscitation. These studies involved predominantly swine models or paediatric populations.

Of particular interest to our proposed study, Paulo et al[9] published safety data from their prehospital service in Italy. They monitored the safety of IO drug administration using the EZ-IO drill between its introduction in 2012 up until 2018. During this period, they recorded 89 administrations without any complications or abnormal drug effects. Van Hoff[10] compared the IV and IO routes using morphine sulphate in a population of cancer patients. They observed no statistically significant differences between IV and IO administration for nearly all of the pharmacokinetic parameters. More recently Barnard et al[11] reported on a series of 34 patients requiring emergency anaesthesia with drugs administered via the IO route, 33 of whom received ketamine. They reported that the IO route was both safe and clinically effective, without any adverse effects. Similarly, Lewis and Wright[12] reported on a series of 1014 IO insertions on 830 combat casualties who required drug therapy. Of these, 745 (61.8%) were used for anaesthetic drugs, and 169 (14%) for analgesic drugs. No major complications were identified; minor complications occurred in just 1.38% of cases and were related to device failure, or extravasation from the insertion site. There were no reports that the device adversely affected the quality of the drug delivered.

Our trial protocol dictates that the trial drug is administered via slow injection (over a maximum period of 5 minutes), thus contact time between the trial drug and the intraosseous catheter is

minimal. We were unable to identify any evidence to suggest that use of an IO catheter impacted the quality of the product being administered. Conversely, we identified several studies indicating the IO route was both safe and clinically effective.

We have completed a risk assessment to determine if the administration of trial drugs via the IO route could reduce the quality of the product. This risk assessment is informed by the following key points:

- The EZ-IO is CE approved specifically for IO drug administration.
- Trial drugs will be in contact with the IO device for a very brief period (5 minutes maximum).

We were unable to identify any literature suggesting IO administration of either morphine sulphate or ketamine hydrochloride reduces the quality or integrity of the drug. We therefore determine that the **likelihood** of the quality of either morphine sulphate or ketamine hydrochloride being adversely affected by IO administration (rather than IV administration) should be categorised as **RARE**.

We have identified literature reporting safe use of both morphine sulphate and ketamine hydrochloride when administered via the IO route. We therefore determine that the **consequence** of administering either morphine sulphate or ketamine hydrochloride via the IO route (rather than IV administration) is **INSIGNIFICANT**.

The resulting risk matrix is detailed below.

	Consequence				
Likelihood	Insignificant	Minor	Moderate	Major	Severe
Almost certain					
Likely					
Possible					
Unlikely					
Rare	**X**				

References

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