Comments on "Nebulised fentanyl for post operative pain relief, a prospective double blind controlled randomised clinical trial"

Sir,

I note the interesting paper by Singh *et al*. on postoperative nebulised fentanyl[1] and offer some comments.

Foremost, the authors are congratulated for their study; it is worthy of further research to refine the technique and develop its utility.

I note that the authors cited our contribution,[2] commenting that the discrepancy between our claim "that inhaled fentanyl, reached to therapeutic level in the blood stream as quickly as intravenous (IV) dosing" and their own findings that IV dosing provided measurably faster pain relief than nebulised dosing of fentanyl. As an aside, we reached similar conclusions using a different technique with morphine,[3] although the two techniques had much in common.

Please note, however, that our studies were performed with pharmacokinetic aims and methods in healthy volunteers, rather than pharmacotherapy of patients with pain. Nevertheless, in terms of blood fentanyl (and morphine) concentrations, the results were as claimed – rapid absorption, high bioavailability – producing a similar profile to IV. So, as suggested by Singh *et al*., how can the discrepancy between their results and our claims be further evaluated? Primarily, by nebulising technique.

Before proceeding, I suspect that the citation of Kissin's paper on pre-emptive analgesia [original 6] is incorrect as this paper did not refer to the pharmacokinetics of intranasal fentanyl. Perhaps Singh *et al*. intended to cite Christrup *et al*.[4] who reported on the similar onsets and durations of analgesia from single doses of intranasal and IV fentanyl.

Although disarmingly simple in concept, aerosol drug delivery is quite complex in theory; even the nebulising technique can vary enormously in practice and thus also in results. In our studies, two different novel proprietary aerosol generators delivered a single dose of the opioid (fentanyl base (100 μg, 50 μL chlorofluorocarbon propellant; morphine sulphate 1.1 mg, 44 μL aqueous solvent) into a single inspiration, followed by a standardised breath-hold before expiration. In the case of fentanyl, the aerosol was generated by the propellant gas pressure in the canister and the actuator of the device;[2] in the case of morphine, by mechanical pressure applied to a "blister" dose package extruding the liquid contents through a very fine mesh.[3] Moreover, a pneumotachograph in each device monitored the inspiration and allowed the dose to be administered only if the inspiratory flow reached coincident preset values (typically 45 L/min and inhaled volume was between 250 and 500 mL). Furthermore, it had previously been established that the techniques generated particles of 50% less than 5-6 μm diameter. Particles too small are generally exhaled; particles too big generally coalesce on mucous membrane surfaces (and this also may coincide with slow rates of drug administration and/or prolonged delivery). The level of experimental control and conditions in our studies ensured that the aerosol particles rapidly reached the alveolar spaces of the lung, and the administered drug behaved more like a gas than a collection of particles. The risk with less control of administration is that the aerosol particles are larger and slower moving, and thus do not reach the alveoli in sufficient proportions, instead simply coating the mucosal surfaces of the oro-pharynx and respiratory tract from whence topical absorption occurs much more slowly than from the alveoli, and with some of the dose being swallowed with much smaller bioavailability. Thus, both the amount and the rate of bioavailability, which are the critical factors for any drug and especially with aerosolised pulmonary administration, are very sensitive to experimental variables.

The paper by Singh *et al*. provides an excellent approach to a practical problem and I look forward to reading more of their progress.

Laurence E Mather

Department of Anaesthesia and Pain Management, Sydney Medical School, The University of Sydney, Sydney, Australia

Address for correspondence:
Emeritus Professor Laurence E Mather, Department of Anaesthesia and Pain Management, Sydney Medical School, The University of Sydney, Sydney, Australia.
E-mail: lmather@med.usyd.edu.au

REFERENCES

1. Singh AP, Jena SS, Meena RK, Tewari M, Rastogi V. Nebulised

fentanyl for post-operative pain relief, a prospective double-blind controlled randomised clinical trial. Indian J Anaesth 2013;57:583-6.
2. Mather LE, Woodhouse A, Ward ME, Farr SJ, Rubsamen RA, Eltherington LG. Pulmonary administration of aerosolised fentanyl: Pharmacokinetic analysis of systemic delivery. Br J Clin Pharmacol 1998;46:37-43.
3. Ward ME, Woodhouse A, Mather LE, Farr SJ, Okikawa JK, Lloyd P, *et al*. Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. Clin Pharmacol Ther 1997;62:596-609.
4. Christrup LL, Foster D, Popper LD, Troen T, Upton R. Pharmacokinetics, efficacy, and tolerability of fentanyl following intranasal versus intravenous administration in adults undergoing third-molar extraction: A randomized, double-blind, double-dummy, two-way, crossover study. Clin Ther 2008;30:469-81.

Access this article online	
Quick response code	Website: www.ijaweb.org
	DOI: 10.4103/0019-5049.130857