Laboratory Investigations

Use of refractometry to identify opioid-containing solutions

Chris J. Eagle MD FRCPC,
J. Roger Maltby MBBS FFARCS FRCPC,
Shellie Kryski BSc, David Hardy PhD MD

The purpose of this laboratory study was to assess the value of refractometry in identifying the contents of a variety of opioid-containing solutions. A hand-held refractometer was used to document the refraction produced by the undiluted contents of alfentanil, fentanyl, morphine, sufentanil ampoules and by solutions of Ringer's lactate, 0.9% saline, 3.3% dextrose in 0.3% saline, and distilled water. Each opioid was then serially diluted in serial 1:2, 1:4, and 1:8 dilutions in each of these solutions and the refractions of each determined. Based on this information, blinded identification of various diluted opioid solutions was attempted. Refractometer values for undiluted fentanyl and sufentanil were identical with those for distilled water. Those for undiluted alfentanil and morphine were almost identical with each other and with 1:2 and 1:4 dilutions of either drug in Ringer's lactate or 0.9% saline. We conclude that refractometry is an unreliable screening method to detect tampering with opioid solutions.

Cette étude réalisée en laboratoire vise à évaluer la valeur de la réfractométrie dans le but d'identifier le contenu de plusieurs solutions contenant des morphiniques. Un réfractomètre portatif est utilisé pour déterminer la réfractions du contenu d'ampoules non diluées d'alfentanil, fentanyl, morphine, sufentanil et de solutés de lactate de Ringer, de physiologique à 0.9%, de dextrose 3,3% dans du soluté salé à 0.3%, et d'eau distillée. Chaque morphinique est ensuite réduit à des dilutions en série de 1:2, 1:4 et 1:8 dans chacun de ces solutés. La réfraction de chacune de ces solutions est déterminée par le réfractomètre. Sur la base de ces renseignements, on essaye d'identifier à l'aveugle chacune des solutions diluées de morphiniques. Les valeurs du fentanyl et du sufentanil purs mesurées par réfractomètrie sont les mêmes que celle de l'eau distillée. Les valeurs de l'alfentanil et de la morphine non dilués sont presque identiques entre elles et avec celles des dilutions a 1:2 et 1:4 de chacune des drogues dans le lactate le Ringer ou de physiologique 0.9%. Nous concluons que la réfractométrie n'est pas une bonne méthode pour détecter la falsification des solution de morphiniques.

Key words
ANALGESICS: abuse, alfentanil, fentanyl, morphine, sufentanil;
MEASUREMENT TECHNIQUES: refractometry.

From the Department of Anaesthesia, Foothills Hospital, University of Calgary, Calgary.

Address correspondence to: Dr. C.J. Eagle, Department of Anaesthesia, Foothills Hospital, Calgary, Alberta, T2N 2T9.

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Abuse of opioids and other substances by anaesthesia personnel is a well-recognized problem.[1,2] Methods employed to achieve control of these substances in operating rooms include individual sign-out kits,[3] opioid dispensing machines,[4] tracking of utilization against anaesthetic records, and analysis of the content of returned syringes.[5] Routine screening of the contents of returned syringes or opened ampoules using gas chromatography mass spectrometric analysis is expensive (C$100 per sample)* and does not eliminate the possibility of diversion of opioids for personal use. Several papers in the pharmacy literature have suggested that refractometry may provide a more efficient and less expensive method of screening large numbers of samples.[5-8] The technique is used in metal working to determine total solutes in aqueous solutions of cutting fluids and quenching solutions used in heat treating.† A refractometer costs approximately C$300, and an operator can perform analyses rapidly (approximately 15 sec per assay) after minimal training.

Previous studies of solutions of opioids and other drugs have shown that simple hand-held refractometers produced reliable, reproducible readings when known concentrations of known drugs were studied.[8] The pur-

*Personal communication. Dr. K. Todd, Director of Laboratories, Foothills Hospital.

†Product monograph. Reichert-Jung refractometer.

pose of our study was to investigate whether refractometry is equally reliable in identifying the unknown contents of opened ampoules or returned syringes. We measured the refractions of various opioids at ampoule concentration and commonly available solutions in the operating room. Refractions were also measured for serial dilutions of each opioid in each solution (0.9% saline, Ringer's lactate, 3.3% dextrose in 0.3% saline (2/3:1/3), and distilled water). Finally, we attempted to identify unknown solutions from their refractometric values.

Methods

The opioids studied were those supplied in narcotic kits to anaesthetists in our hospital.[9] These are alfentanil 500 $\mu g \cdot ml^{-1}$,* fentanyl 50 $\mu g \cdot ml^{-1}$,* sufentanil 50 $\mu g \cdot ml^{-1}$,* and morphine 10 $mg \cdot ml^{-1}$†. Refractometric values were obtained using a hand-held refractometer (Reichert-Jung model 10441). This device is temperature-compensated and measures refraction on a 10 degree (Brix) scale with an accuracy of 0.25 degrees. Calibration is confirmed by determining the refractometric value of distilled water (zero degrees). This device does not provide a direct assessment of the refractive index but only a comparison with distilled water.

Refractometric values were obtained by three observers. Each observer measured refraction on two samples of each undiluted opioid solution and on two samples of each of Ringer's lactate, 0.9% saline, 2/3:1/3, and distilled water. Weaker opioid solutions were prepared by making 1:2, 1:4 and 1:8 dilutions of each of the opioids with each of the diluent solutions. Six samples of each opioid at each dilution in each solvent were made. Each observer measured refraction of two samples at each dilution. Finally, "tampered" solutions were prepared by the pharmacy department for identification of their contents by a blinded observer.

Results

The refractometric values of the undiluted opioid solutions, diluent solutions and diluted opioid solutions are shown in Table I. Undiluted fentanyl, sufentanil and distilled water all produced zero degrees refraction. Undiluted morphine and alfentanil produced refractometric values which were clearly different from those of fentanyl, sufentanil and distilled water, but not greatly different from each other. Although alfentanil and morphine have similar refractive measures, they are significantly different ($P < 0.05$, Student's t test). Serial dilution of morphine or alfentanil with either Ringer's lactate or 0.9% saline produced such small decreases in measured refraction that dilutions of 1:2 or even 1:4 might go undetected. Typical dilution curves are shown in Figures 1 and 2. The refractometric values of the "tampered" solutions shown in Table II demonstrate the range of possible identities for each solution, its actual contents, and its concentration.

Discussion

Our measurements are consistent with those of earlier studies[5-8] which described the use of refractometry by hospital pharmacies as part of their control systems in screening opioid-containing solutions. Most such studies have concluded that refractometry is a useful adjunct to preexisting control systems, specifically for the detection of opioid diversion. Deficiencies, such as the inability to distinguish sterile water from fentanyl or sufentanil, have been discounted in somewhat cavalier fashion.[6] Our aim was to construct a series of "standard curves" and then to see if "unknown" solutions could be identified from the curves in a manner that would be used in a pharmacy department. Although there are anecdotal reports of refractometry to identify diversion of drugs by anaesthetists,[6] once a knowledgeable individual is aware of the screening method employed he or she can create mixtures to simulate the refractometry results for a given opioid.

The reason that solutions of different drugs and a variety of diluents have similar refractometric values is that the refractive index is dependent solely upon the electron density in the material and the resonant frequency of those electrons. Clearly, all materials or solutions in which these physical properties are approximately equal will have similar indices of refraction. Because the refractive index is only a function of the electron density and their resonant frequency, refractometry cannot be used to identify the presence or absence of a specific substance, for example, an opioid. Full understanding of the theoretical explanations of refraction is not essential for the clinical anaesthetist to recognize the serious deficiencies of refractometry as a screening mechanism for misuse of narcotics by anaesthetists or other operating room personnel. Our results demonstrate that solutions can be prepared using readily available diluents whose refractometric values match those of the undiluted opioids commonly used by anaesthetists. Thus the refractometer can be used to determine the concentration of a known opioid in a known solvent, but cannot be used to determine the concentration of an unknown opioid in an unknown solvent.

Effective monitoring of narcotic use by anaesthesia personnel is difficult. Despite elaborate sign-out procedures, narcotic-dependent practitioners can still divert opioids intended for patients for their personal use. Continuous observation and mandatory urine testing for controlled substances might result in assurance of control, although

*Janssen Pharmaceutica, Inc.
†Abbott Laboratories, Ltd.

TABLE I Refractometer readings of identified solutions (mean ± SD)

Drug	*Dilution*	*0.9% Saline*	*Distilled water*	*2/3:1/3*	*Ringer's lactate*
Morphine	Undiluted	1.33 ± 0.13	1.33 ± 0.13	1.33 ± 0.13	1.33 ± 0.13
	- 1:2	1.25 ± 0.00	0.83 ± 0.13	2.32 ± 0.14	1.25 ± 0.00
	- 1:4	1.18 ± 0.07	0.40 ± 0.09	2.58 ± 0.26	1.23 ± 0.03
	- 1:8	1.07 ± 0.05	0.33 ± 0.13	2.92 ± 0.13	1.22 ± 0.03
	Diluent alone	1.00 ± 0.00	0.00 ± 0.00	3.25 ± 0.00	1.22 ± 0.03
Fentanyl	Undiluted	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	- 1:2	0.54 ± 0.06	0.00 ± 0.00	1.33 ± 0.26	0.46 ± 0.06
	- 1:4	0.75 ± 0.00	0.00 ± 0.00	2.10 ± 0.27	0.71 ± 0.06
	- 1:8	1.00 ± 0.00	0.00 ± 0.00	2.58 ± 0.26	0.92 ± 0.13
	Diluent alone	1.00 ± 0.00	0.00 ± 0.00	3.25 ± 0.00	1.12 ± 0.11
Sufentanil	Undiluted	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	- 1:2	0.50 ± 0.00	0.00 ± 0.00	1.37 ± 0.29	0.38 ± 0.19
	- 1:4	0.75 ± 0.00	0.00 ± 0.00	2.22 ± 0.18	0.67 ± 0.13
	- 1:8	0.90 ± 0.09	0.00 ± 0.00	2.67 ± 0.13	0.82 ± 0.07
	Diluent alone	1.00 ± 0.00	0.00 ± 0.00	3.25 ± 0.00	1.12 ± 0.11
Alfentanil	Undiluted	1.22 ± 0.02	1.22 ± 0.02	1.22 ± 0.02	1.22 ± 0.02
	- 1:2	1.22 ± 0.02	0.62 ± 0.11	2.12 ± 0.11	1.12 ± 0.11
	- 1:4	1.00 ± 0.00	0.35 ± 0.12	2.45 ± 0.16	1.12 ± 0.11
	- 1:8	1.00 ± 0.00	0.16 ± 0.17	2.83 ± 0.13	1.12 ± 0.11
	Diluent alone	1.00 ± 0.00	0.00 ± 0.00	3.25 ± 0.00	1.12 ± 0.11

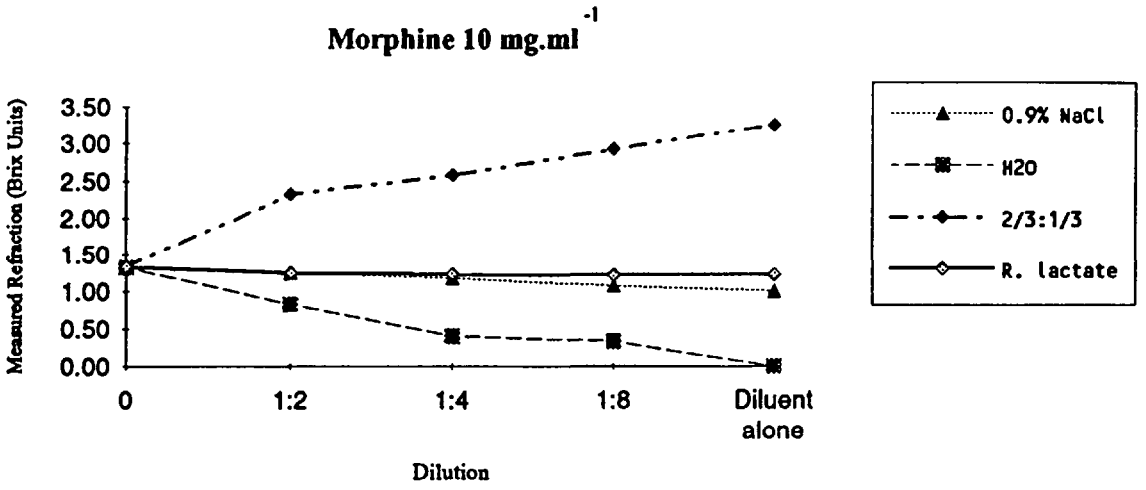

FIGURE 1 Measured refraction of morphine at progressive dilutions.

a clever, well-informed addict would likely be able to circumvent both of these. Awareness that there is ongoing analysis of the contents of returned syringes might have some value, although the expense of quantitative analysis makes it likely that only occasional random spot checks could be performed. A cheaper method of analysis thus has some appeal.

One pharmacy department[6] recommends that routine dilution of alfentanil should prompt the narcotic control official to question the anaesthetist about the need for such dilution. Given the documented advantages of opioid infusions over bolus injections, we view this as an inappropriate and restrictive policy. Further, it recommended that information about the limitations of refractometers should only be disseminated to "other health care professionals on an as-needed basis."[6] While opioid abuse is a serious issue for anaesthetists, we feel that, given the evident limitations of refractometry, such an attitude is not justified. If the technique itself cannot distinguish between distilled water and either fentanyl or

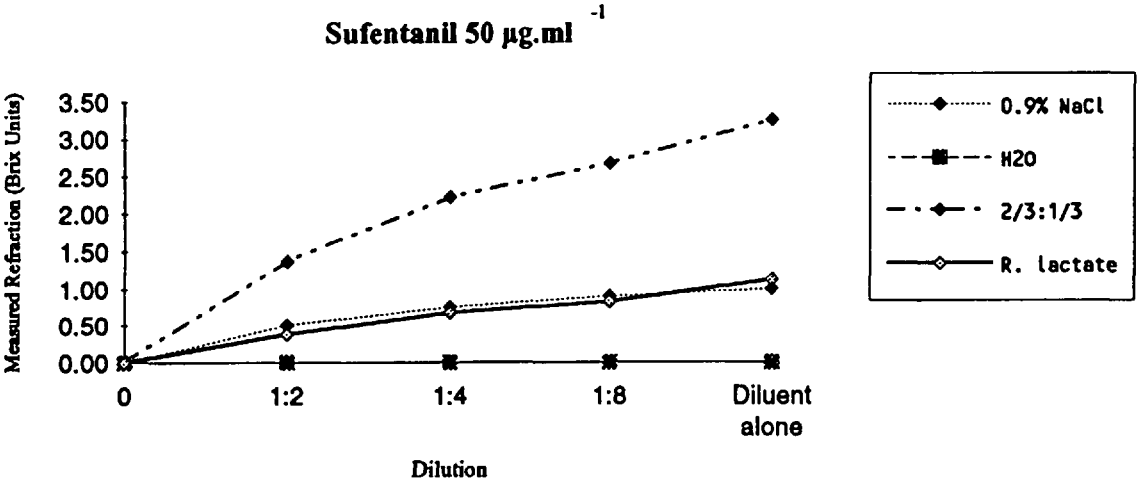

FIGURE 2 Measured refraction of sufentanil at progressive dilutions.

TABLE II Refractometric analysis of unknown solutions

Refraction	*Actual content*	*Possible contents*	
0.50	Sufentanil 25 µg · ml^{-1} in R.L. (1:2)	1 Fentanyl 50 µg · ml^{-1} in R.L.	1:2 diln.
		2 Fentanyl 50 µg · ml^{-1} in N.S.	1:2 diln.
		3 Sufentanil 50 µg · ml^{-1} in N.S.	1:2 diln.
		4 Sufentanil 50 µg · ml^{-1} in R.L.	1:2 diln.
0.50	Fentanyl 25 µg · ml^{-1} in R.L. (1:2)	1 Fentanyl 50 µg · ml^{-1} in R.L.	1:2 diln.
		2 Fentanyl 50 µg · ml^{-1} in N.S.	1:2 diln.
		3 Sufentanil 50 µg · ml^{-1} in N.S.	1:2 diln.
		4 Sufentanil 50 µg · ml^{-1} in R.L.	1:2 diln.
1.10	Alfentanil 125 µg · ml^{-1} in N.S. (1:4)	1 Ringer's lactate	
		2 Morphine 10 mg · ml^{-1} in N.S.	1:8 diln.
		3 Alfentanil 500 µg · ml^{-1} in R.L.	1:8 diln.
1.20	Morphine 1.25 µg · ml^{-1} in R.L. (1:8)	1 Alfentanil 500 µg · ml^{-1}	
		2 Alfentanil 500 µg · ml^{-1} in R.L.	1:2 diln.
		3 Alfentanil 500 µg · ml^{-1} in N.S.	1:2 diln.
0.75	Fentanyl 12.5 µg · ml^{-1} in R.L. (1:4)	1 Morphine 10 mg · ml^{-1} in H_2O	1:2 diln.
		2 Sufentanil 50 µg · ml^{-1} in N.S.	1:4 diln.
		3 Sufentanil 50 µg · ml^{-1} in R.L.	1:4 diln.
		4 Fentanyl 50 µg · ml^{-1} in N.S.	1:4 diln.
		5 Fentanyl 50 µg · ml^{-1} in R.L.	1:4 diln.
1.10	Alfentanil 62.5 µg · ml^{-1} in R.L. (1:8)	1 Ringer's lactate	
		2 Morphine 10 mg · ml^{-1} in N.S.	1:8 diln.
		3 Alfentanil 500 µg · ml^{-1} in N.S.	1:2 diln.
2.75	Morphine 2.5 µg · ml^{-1} in 2 in 3:1 in 3 (1:4)	1 Fentanyl 50 µg · ml^{-1} in 2/3:1/3	1:8 diln.
		2 Sufentanil 50 µg · ml^{-1} in 2/3:1/3	1:8 diln.
0.00	Sufentanil 50 µg · ml^{-1}	1 Distilled water	
		2 Fentanyl 50 µg · ml^{-1}	
		3 Sufentanil 50 µg · ml^{-1}	

sufentanil, it will be of little use in detecting the diversion of either of those drugs. Likewise, unjustified suspicions and even accusations may be encountered when syringes are contaminated with propylene glycol (creating non-homogeneity), or syringe contents have been inadvertently diluted by flushing of intravenous lines.[7]

We conclude that the nature of refraction of light makes the refractometer an unreliable instrument for analysis of "tampered" contents of syringes or ampoules. It is not designed for this purpose and is unlikely to detect diversion of narcotics by the misuser who makes clever substitutions in the contents of opened ampoules or returned syringes. Although refractometry has been recommended for routine monitoring of controlled substances by hospital pharmacies, we doubt whether its use will result in better narcotic control or earlier detection of drug-dependent individuals.

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