

PAIN ON I.V. INJECTION OF SOME ANAESTHETIC AGENTS IS EVOKED BY THE UNPHYSIOLOGICAL OSMOLALITY OR pH OF THEIR FORMULATIONS

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SUMMARY

We have studied the intensity and time-course of pain during and after injection into an isolated vein segment in seven normal subjects of saline or glucose of different osmolalities (0-6 osmol kg⁻¹) or pH (2-13). Pain scores were recorded continuously by a modified visual analogue scale apparatus. With osmolar stimulation, pain occurred at 1.0 osmol kg⁻¹ during perfusion and 3.0 osmol kg⁻¹ with rapid injection and increased with osmolar concentration of both saline and glucose solutions. Acidic and alkaline solutions evoked pain at a pH value < 4 or > 11. We conclude that pain on i.v. injection of some sedative and hypnotic drugs is likely to be caused by formulations of extremely unphysiological osmolalities or pH values.

KEY WORDS

Anaesthetics, intravenous. Complications: pain on injection, pH, osmolality.

The principal stimulus that evokes pain on i.v. injection of some agents used as supplements for anaesthesia is still unknown. The importance of osmolality is suggested by the reported venous sequelae following x-ray phlebography. The incidence of pain on injection and thrombotic complications appear to be lower with x-ray contrast media of low osmolality [1, 2]. Although the relationship between i.v. osmolality and pain intensity has not been examined systematically, the incidence of pain seems to increase at osmolalities greater than 1 osmol kg⁻¹.

In view of these findings, it is surprising that little attention has been paid to the fact that a number of anaesthetic agents evoking pain on injection are used in formulations of extremely unphysiological osmolality. For example, diazepam [3, 4] and etomidate [5] are dissolved in

solutions of osmolalities more than 10-fold that of blood [6]. Finally, painful injections are reported for agents such as methohexitone and thiopentone [7], vecuronium and nalbuphine, although they are used in formulations of less than 0.8 osmol kg⁻¹. According to our own measurements, the formulations of these drugs have an unphysiological pH. Methohexitone and thiopentone are rather alkaline (pH 11.5-12.2, depending on the solvent) and vecuronium and nalbuphine are acidic (pH 4.1 and pH 3.5, respectively).

To test the hypothesis that the osmolality or pH of anaesthetic drug formulations is the principal stimulus causing pain, we have administered solutions of varying osmolality or pH into a segment of a dorsal hand vein. We were particularly interested to identify the threshold concentrations at which pain occurred.

SUBJECTS AND METHODS

Seven healthy subjects (authors and medical students) volunteered and consented to this study, which was approved by the Committee on Medical Ethics of the University of Düsseldorf. Experiments started at 09:00 with the subjects sitting comfortably semi-recumbent at a thermoneutral room temperature of 25 °C.

A vein segment, free of side branches, between two valves was identified on the dorsum of the non-dominant hand. Two Teflon cannulae (Venflon 2, Viggo AB) were inserted from distant proximal and distal puncture sites (fig. 1), thus permitting the vein segment to be isolated from the systemic circulation by external occluders.

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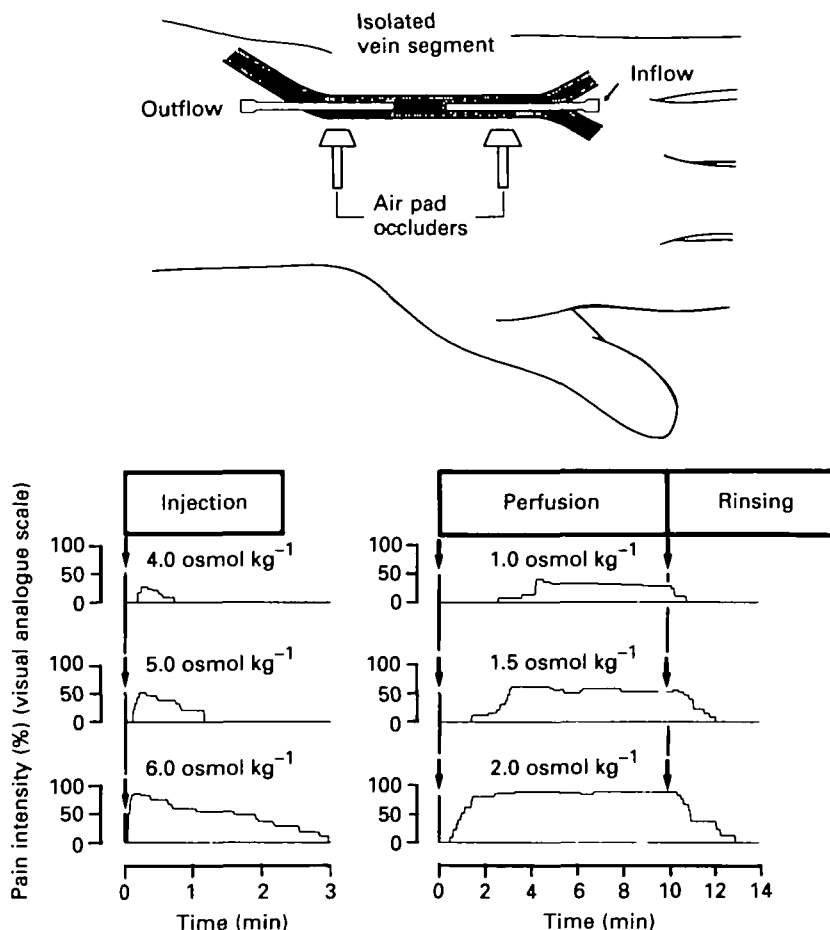


FIG. 1. Scheme of selective perfusion of an isolated vein segment in man and original pain intensity recordings. Injection: hyperosmolar sodium chloride (pH 7.4) 1 ml in 1 s, 35 °C. Perfusion: hyperosmolar sodium chloride (pH 7.4) 1.5 ml min⁻¹, 35 °C. Rinsing: 0.9% sodium chloride (iso-osmotic) (pH 7.4) 1.5 ml min⁻¹, 35 °C. From such pain recordings were obtained latency, maximum, time to maximum, half-life to maximum pain and time to recovery for the perfusion experiment. As is apparent from this example, pain intensity and duration of pain increased while latency decreased with injections of increasing osmolalities. During constant perfusion, pain intensity increased with higher osmolalities also and attained a stable plateau.

With the cannulae in place, the hand was raised on a cushioned holder above heart level so that the hand veins were almost empty at all times, in order to minimize dilution or buffering of the test solutions by blood.

Subjects rated pain intensity on a modified visual analogue scale with the help of an apparatus of our own design. A handle, connected to a linear potentiometer, could be moved over a distance of 80 mm from the left (no pain) to the right (maximally tolerable pain), yielding a voltage proportional to the rated pain intensity between 0 (no pain) and 100% (tolerance maximum). The

voltage was recorded continuously on a Gould TA 500 Polygraph so that it was possible to follow not only the intensity, but also the time-course of the evoked pain (fig. 1).

Hyperosmolar saline and glucose solutions were prepared at concentrations of 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 osmol kg⁻¹ at constant pH (7.4). Saline solutions of pH between 2–13 were prepared by adding sodium hydroxide or hydrochloric acid. The osmolality was constant (0.3 osmol kg⁻¹) at each pH.

For i.v. block, procaine concentrations between 0.1 and 1.0% ($3.7\text{--}36.7 \times 10^{-3}$ mol litre⁻¹) in steps

of 0.2% were prepared with Tyrode's solution at osmolar concentrations between 0.29 and 0.30 osmol kg⁻¹ at pH 7.4.

All solutions were given i.v. at 35 °C (the temperature of blood in cutaneous hand veins).

Each subject was studied twice on different days separated by 1–2 weeks. On one day the vein was exposed to varying osmolalities, and on the other to varying pH. To avoid the influence of possible long-term tissue alteration at the sensory structures of the vein wall, venous segments were not used twice.

The collapsed vein segment was perfused continuously with saline (pH 7.4, 0.3 osmol kg⁻¹, 35 °C, rate 3 ml min⁻¹) in order to simulate injections into a normally patent vein. In each subject, the study sequence was as follows: during a control period of 10 min, the vein segment was perfused continuously with iso-osmotic saline (3 ml min⁻¹); during saline perfusion, 1 ml of the test solutions of different osmolality or pH was injected at random within 1 s. Each concentration was administered twice in any experiment.

With the vein segment separated from the systemic circulation by external air pad occluders, the isolated segment was perfused continuously at constant osmolality of 1.0, 1.5 and 2.0 osmol kg⁻¹ at 1.5 ml min⁻¹ for 10 min each, and thereafter rinsed with iso-osmotic saline.

The perfusion experiment was repeated on a separate day using glucose solution in equal osmolar concentrations in three subjects.

Isolation of the vein segment during the experiment was confirmed by the absence of erythrocytes in the effluent perfusate and by identical osmolalities of the in- and outflowing solution.

After the test injections were completed, the isolated vein segment was perfused continuously with procaine. Starting with 0.1 and 0.2%, the procaine concentrations were increased in steps of 0.2% and maintained at a given concentration for 10 min each. The subjects' maximal pain rating to a painful stimulus of constant osmolality and volume was evaluated before procaine and during the last 1 min of perfusion at each given concentration of procaine. Thereafter, the vein segment was rinsed with saline until pain intensity reached control values.

Latency, maximum pain intensity and duration were evaluated from the recordings (fig. 1). Concentration–effect curves were plotted for each subject by relating the osmolality or pH to the

subjects' maximum pain intensity in injection and in perfusion experiments.

The latencies (time from exposure to drug to occurrence of pain), durations and times to maximum evoked pain sensation were tabulated as means and ranges. For the perfusion experiments, the half-lives to maximum and to recovery (time from the start of sensation to 50% of maximum pain and time from the start of rinsing to 50% of recovery, respectively) were tabulated also.

RESULTS

Pain occurred earlier as the osmolalities increased in both the injection and the perfusion experiment. With the injections, pain was transient and subsided within 2–5 min. In contrast, during

TABLE I. Time course (mean (range)) of pain following injections of saline with varying osmolality and pH. Data from seven subjects with hyperosmolar and three subjects with acidic and alkaline stimulation

	Pain		
	Latency (s)	Duration (s)	Time to maximum (s)
Hyperosmolar saline			
Osmolality (osmol litre ⁻¹)			
3.0	13 (12–15)	31 (0–51)	22 (17–33)
4.0	10 (7–12)	50 (21–60)	28 (18–39)
5.0	7 (5–9)	74 (32–101)	32 (16–40)
6.0	5 (4–6)	135 (52–262)	34 (11–59)
Acid saline			
pH			
3.5	8 (7–14)	15 (0–23)	14 (12–16)
3.0	6 (5–9)	23 (16–28)	14 (8–18)
2.5	5 (4–9)	45 (32–56)	14 (11–19)
2.0	4 (3–6)	68 (55–82)	12 (9–16)
Alkaline saline			
pH			
11.5	9 (7–12)	11 (0–15)	13 (9–16)
12.0	6 (4–8)	65 (15–137)	18 (9–29)
12.5	4 (3–6)	110 (30–226)	9 (5–15)
12.0	3 (3–5)	282 (252–312)	7 (4–10)

TABLE II. Time-course (mean (range)) of pain during hyperosmolar saline perfusion. Data from seven subjects

Osmolality (osmol litre ⁻¹)	Pain during perfusion and rinsing			
	Latency (s)	Time to maximum (s)	Half-life (s)	
			To maximum	To recovery
1.0	223 (75–378)	405 (252–528)	106 (42–153)	32 (8–48)
1.5	95 (36–168)	304 (189–414)	71 (42–96)	41 (12–78)
2.0	30 (6–78)	195 (96–363)	69 (24–180)	82 (15–180)

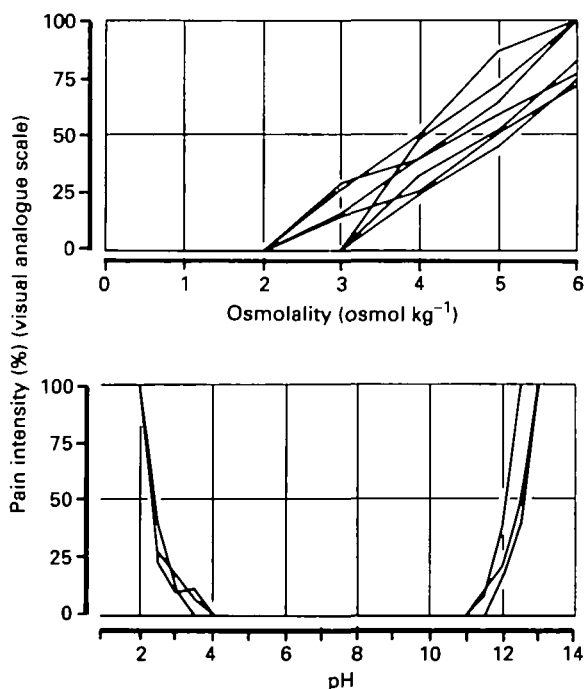


FIG. 2. Pain intensity–concentration relationships with injections of varying osmolalities or pH. Data from all seven subjects with osmolar stimulation (above) and from three subjects exposed to alkaline and acid saline (below). Note that, above the individual thresholds, pain intensity increased only with increasing osmolalities, but with both increasing and decreasing pH.

constant perfusion, pain intensity at a given concentration was maintained until the pain-evoking solution was washed away.

For injections of varying osmolality and pH, the temporal variations between stimulus ap-

plication and pain are summarized in table I. The latencies decreased from 13 s at the least to 5 s at the greatest osmolality, while the times to maximum pain did not change with stimulus strength. The duration of pain varied markedly between subjects (e.g. 52–262 s with the injection of 6.0 osmol kg⁻¹), but increased with greater osmolality in each subject.

In the case of the pH stimulus, pain lasted at least 250 s after injection of alkaline solution (pH 13)—much longer than after the injection of acidic saline (55–82 s). The latencies decreased with both acidity (from 8 to 4 s) and the basicity of the injectate (from 9 to 3 s).

The perfusion experiments (table II) revealed a close relationship between stimulus strength and the time-course of pain as both the latencies and times to maximum pain decreased with increasing osmolality. The half-lives to maximum pain and to recovery reached similar values with the greatest osmolality.

Injections with hyperosmolar saline evoked pain whenever the osmolality exceeded 3.0 osmol kg⁻¹. As shown by each subject's concentration–effect relationship in figure 2, pain intensity increased almost linearly with the osmolality of the test solution. The minimal osmolality that just evoked pain (pain threshold) was 3.0 in four subjects and 4.0 osmol kg⁻¹ in the remaining three. Maximum pain occurred at approximately 6.0 osmol kg⁻¹, with which pain intensities ranged between 72 and 100% (100% = tolerance maximum) of the intensity scale, while two subjects rated their pain as intolerable. It should be noted that hypo-osmolar solution (distilled water) did not evoke pain.

Solutions of both high acidity and high alkalinity evoked pain at the extreme ends of the pH

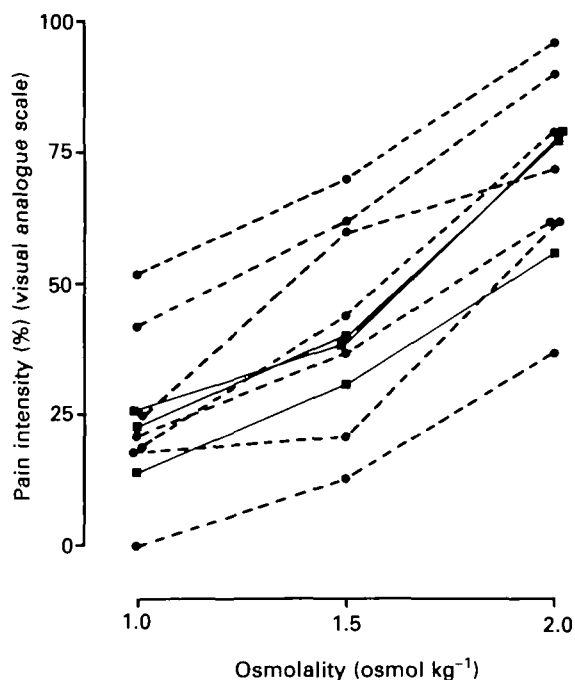


FIG. 3. Pain intensity–osmolality relationships during continuous perfusion. Saline was used in all seven subjects (●) and additionally glucose (■) in three of the subjects. Note that above threshold pain intensity always increased with increasing osmolality. Note also the congruency of pain intensity–concentration curves for saline and glucose.

scale ($\text{pH} \leq 4$ and $\text{pH} \geq 11$). The intensity of pain increased as the pH increased to more than 11 or decreased to less than 4 (fig. 2). Tolerance maxima were reached at a pH of 2 and 13, respectively. The subjects rated the pain as intolerable with three of six injections.

Because of severe sequelae described below, the pH effects were studied in three subjects and with injections only.

Constant perfusion of the isolated vein segment with hyperosmolar concentrations evoked pain at lower thresholds ($1.0 \text{ osmol kg}^{-1}$) than with injections ($3.0 \text{ osmol kg}^{-1}$) (fig. 3). Concentrations less than $1.0 \text{ osmol kg}^{-1}$ did not cause pain even when the perfusion time lasted 10 min. Pain intensity increased almost linearly with osmolality in the range 1.0 – $2.0 \text{ osmol kg}^{-1}$, but differed markedly between subjects. No difference occurred in pain intensity–concentration relationships between saline and glucose.

With increasing i.v. concentrations of procaine, pain intensity decreased, even though the stimulus strength of the injectate ($6.0 \text{ osmol kg}^{-1}$) was the

same as before local anaesthesia. Pain on injection disappeared completely at an i.v. concentration between 0.4% ($14.7 \times 10^{-3} \text{ mol litre}^{-1}$) and 0.8% ($29.4 \times 10^{-3} \text{ mol litre}^{-1}$), in five of the seven subjects at 0.6% ($22 \times 10^{-3} \text{ mol litre}^{-1}$) and recurred within 10 min during rinsing. It should be stressed that i.v. administration of procaine did not block sensation of the overlying skin as tested by mechanical (touch, pinprick) and thermal (warm, cold) stimuli.

All subjects described the evoked pain as dull, burning, oppressive and highly unpleasant. Low intensity pain was localized by the subjects at the site of injection of the isolated vein segment but, with intensities greater than 70 % of the tolerance maximum, pain extended from the site of injection to the whole dorsum of the hand, extensive areas of the forearm, and sometimes also the palm of the hand.

Every subject suffered small to moderately painful venous sequelae up to 24 h after the experiment, characterized by increased sensitivity to touch and by cutaneous flush. In five of the seven subjects, the veins became indurated for up to 4 weeks, but thereafter regained normal appearance and function.

After injection of acidic and alkaline solutions, perivenous oedema developed immediately and was followed by a thrombophlebitis for up to 3 weeks. These sequelae were not confined to the perfused vein segment, but spread over the dorsum of the hand and parts of the forearm. For ethical reasons, we refrained from further experiments on pH effects, in particular those with constant perfusion.

DISCUSSION

Both the osmolar concentration and pH of solutions brought into contact with the intact intima of a superficial hand vein were factors determining the evocation of pain.

We believe our methods ensured that the intima, the only layer between blood and the subendothelially-located receptive endings [8], was intact, that the dilution and buffering of the test solutions by blood was avoided or at least minimized and that, during the procaine experiments, procaine did not enter the systemic circulation. These precautionary aims were met by injecting the test solution into a collapsed vein segment devoid of branches via a smooth Teflon cannula placed into that segment from distant

puncture sites that could not be reached by the solutions. The proximal cannula, used as the inflow path, prevented blood from entering the segment; the valves prevented retrograde outflow. When the test solutions were injected (1 ml within 1 s), the dilution by the continuous infusion of saline 3 ml min^{-1} and by the remaining blood flow was comparable to the clinical situation when drugs are injected into an infusion. In this case, the exact i.v. osmolality and pH were uncertain. However, the i.v. concentration was certainly constant during perfusion, as the measured osmolality of the effluent perfusate differed by not more than 3% of the inflow solution.

Continuous recording of the subjects' pain ratings via the modified visual analogue scale made it possible to judge both the intensity and the time-course of the evoked pain. Two observations are worthy of note. First, the same concentrations were rated as almost equally painful on repeat administration with intra-individual differences of less than 10% of the visual analogue scale. Second, at constant osmolar concentrations during perfusion, the plateau of the pain intensities did not change while the stimulus strength was maintained constant for 10 min (fig. 1). This is noteworthy because cutaneous nociceptors are known to adapt within seconds when stimulated with constant noxious pressure or heat [9]. This observation and the fact that randomly varied concentrations gave highly repeatable results with only minimal variations in pain intensity, support our contention that subjective pain rating is a reliable and reproducible index from which to derive concentration–effect relationships.

Above the individual thresholds, pain intensity increases almost linearly up to a certain maximum. Regardless of threshold differences between the subjects, the ranges of osmolality (3.0–6.0 osmol kg^{-1}) and pH (4.0–2.0 and 11.0–13.0) which evoked pain were often less than that of commercially available drug solutions known to cause pain on injection. For example, diazepam and etomidate are used in formulations of 7.8 and 5.0 osmol kg^{-1} [6]. Pain on injection of these drugs is therefore likely to be the consequence of the extreme osmolalities and pH values of their conventional formulations.

Consistent with this view, the incidence of pain on injection was reduced to less than 1% with new emulsion formulations of diazepam and etomidate [3, 7, 10] which have osmolalities near that of blood [6].

It is worthy of note that the principal pain-evoking stimulus is the osmolar concentration rather than the ionic strength of the injectate. This is shown by the pain intensity–concentration relationships for both hyperosmolar saline (strong electrolyte, ionic dissociation near 100%) and glucose (weak electrolyte, ionic dissociation near 0%) in figure 3.

During constant perfusion of vascularly isolated vein segments, pain occurred and attained its maximum more quickly and lasted longer during the rinsing period as the osmolar concentrations increased. Also, at a given concentration, pain intensity did not change with time, but disappeared within 3 min during rinsing. Thus, in the absence of adaptation, pain depends on the osmolar concentration present in a vein at a given time, which in turn depends on the volume in and the flow of blood through this vein. The highly variable incidence of painful injections reported in clinical studies [3–5, 7] and its occurrence in particular with injections into small calibre veins is therefore not unexpected. In addition, the incidence of pain on injections may be underestimated in the case of hypnotic agents because patients are likely to lose consciousness before pain can be perceived—we found latencies to perception of pain of up to 30 s (tables I, II).

As i.v. procaine abolished pain on injection completely without numbing the skin above the perfused vein, the painful sensations from veins probably originate from neuronal elements within their walls, possibly the free afferent nerve endings between the media and intima [8]. As the transduction processes at the receptor membrane are less vulnerable to pharmacological interventions than the axonal conduction process [11], it is likely that procaine blocked nerve conduction. The pain conducting axons probably belong to the myelinated A δ group, because pain was abolished at the same concentrations of procaine (0.4–0.8%) that abolished spike activity of thinly myelinated vagal afferents of the heart [12].

In conclusion, solutions with osmolalities $> 1.0 \text{ osmol kg}^{-1}$ and pH either < 4 or > 11 evoke pain on injection into veins at the dorsum of the hand of humans. This explains the high incidence of painful injections with several drugs which are used in formulations with extremely unphysiological osmolalities or pH. Pain on injection and perhaps also thrombophlebitis can probably be avoided by diluting hyperosmolar drug formu-

lations with distilled water or by aspirating blood for buffering into formulations with extreme pH just before injection.

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