The effects of intrathecal midazolam on sympathetic nervous system reflexes in man—a pilot study

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1 Nine patients were given intrathecal injections of midazolam (dose 0.3–2 mg dissolved in 3 ml 5% dextrose). No changes in motor power or general sensation were produced. Resting heart rate and blood pressure were unchanged and normal valsalva manoeuvres were elicited 30 min post-injection. Cardiovascular responses were provoked at a light plane of anaesthesia by intubation of the trachea and manipulation of peritoneum and bowel but not by surgical incision of the skin. Intrathecal administration of midazolam relieved post-operative pain of somatic origin but not of visceral origin.

2 It is concluded that intrathecal midazolam in the dosage used interrupts somatic nociceptive afferent pathways but not abdominal visceral nociceptive afferent pathways.

Keywords midazolam intrathecal injection reflexes

Introduction

It has been suggested that large intravenous doses of benzodiazepines suppress sympathetic nervous system responses to noxious stimuli (Boralessa *et al.*, 1983). Intrathecal administration of the water soluble imidazo-benzodiazepine midazolam (Hypnovel, Roche) interrupts somato-sympathetic reflexes in the anaesthetised dog (Whitwam *et al.*, 1982; Niv *et al.*, 1983). Abolition of the reflex evoked by electrical stimulation of nerves in the hind leg but not the foreleg by lumbar intrathecal injection suggests that the site of action was the dorsal horn of the lumbar spinal cord rather than rostral spread or a local anaesthetic effect on nerves entering the spinal cord. A receptor mechanism was also indicated by the reversal of the inhibition by the benzodiazepine antagonists RO 15-1788 and RO 15-3555.

Epidural midazolam has been reported to produce post-operative analgesia (Rigoli, 1983). No evidence for a spinal site of action of the drug was produced in this study and the incidence of side effects, particularly sedation, was high.

A peptide which stereo-specifically binds to benzodiazepine receptor preparations has been found in human cerebrospinal fluid (Deckert *et al.*, 1984), confirming the existence of endogenous benzodiazepine-like substances (Whitwam, 1983). Naturally-occurring benzodiazepine antagonists, the β -carboline, have been known for some time (Braestrup & Nielsen, 1981).

When one couples this knowledge with the demonstration of benzodiazepine stereospecific binding sites in the spinal cord (Mohler & Okada, 1977) and brain (Schoch *et al.*, 1985) it seems likely that there exists a neurotransmission system involving benzodiazepine-like peptides interacting with receptors in the spinal cord. This evidence points to a possible spinal mechanism which may be the site of action of midazolam in producing analgesia (Rigoli, 1983) and interruption of somato-sympathetic reflexes (Whitwam *et al.*, 1982; Niv *et al.*, 1983). Therefore, it was decided to perform the present investigation in man as a pilot study to define the dose of intrathecal midazolam necessary to elicit effects

on sympathetic reflexes evoked by surgery, and to see if these effects correlated with painful sensations post-operatively.

Methods

The study was approved by the Medical Ethics Committee of the Leeds Western District Health Authority and informed consent was obtained from all patients. Nine patients (seven female, two male, ASA I or II) were used for the study (Table 1). Pre-medication was diazepam 0.2 mg kg⁻¹ orally, 1 h prior to the study. Seven patients were scheduled for intra-abdominal (colo-rectal) surgery and two for surgery on the leg. Seven patients were monitored invasively; blood pressure (BP) was monitored directly via a 20 gauge cannula (Angiocath) introduced into the radial artery of the non-dominant hand (Allen's test was used to test for the integrity of the deep palmar arch) and central venous pressure (CVP) was monitored via a catheter (Drum Cartridge) introduced into an antecubital vein. The ECG, BP and CVP were monitored continuously and recorded with a 4-channel chart recorder (Phillips) and tape recorder (Racal Store 4). After a period of 10 min baseline cardiovascular measurements were made.

In the other two patients BP was monitored using an oscillotonometer and the ECG was also

recorded. In all patients a peripheral intravenous infusion (*running at a slow rate*) was established prior to insertion of a 20 gauge spinal needle into the lumbar subarachnoid space (L2/3 or L3/4) under aseptic conditions with the patient in the left lateral position. A quantity of midazolam (see Table 1) was then dissolved in 5% dextrose to final volume of 3 ml; this was injected into the subarachnoid space over a period of 5 s with no barbotage. The patients were then immediately placed in the supine position. BP, ECG and CVP were continuously monitored for 30 min in invasively monitored patients. In the other patients, ECG was monitored continuously and BP measured every 2 min. During the 30 min period after the subarachnoid injection of midazolam, detailed sensory testing was performed on the skin of the legs. The sensations tested were: light touch, deep pressure, joint position sense and painful sensations produced by sharp pin prick and intradermal injection of 0.5 ml of saline. Motor power and heel/toe co-ordination were also tested and at the end of the 30 min period an attempt was made to define a dermatomal level for changes in sensations evoked by pin prick and intradermal injection of saline. The patients who were invasively monitored then performed another Valsalva manoeuvre to test the integrity of autonomic nervous system function.

Table 1 Details of patients included in the study: dose of subarachnoid midazolam and quantity of opioid analgesia required

	1†	2†	3†	4†	Subject 5	6†	7†	8	9†
Age (years)	49	76	41	78	24	20	42	27	78
Weight (kg)	49.4	48	73.5	66.7	46.7	61	46	90	65
Surgery	A	A	A	A	A	A	L	L	A
Midazolam dose (mg)	2	0.3	1.5	1	2	0.75	0.5	2	1.5
Intraoperative opioid received—diamorphine (mg)	2*	0*	0*	0*	1.5*	0*	0*	0	1*
Post-operative opiate received—paparavetum mg in first 48 h post op	40	20	60	50	70	105	0	0	40
Initial dermatomal pin prick level of change in sensation evoked by:	T6	T4	T4	C4	T5	—	T4	—	T5
intradermal injection of saline	T6	T10	T4	C4	T9	T5	T4	T5	T8

A = intra abdominal surgery

L = surgery on the legs (patient 7 also had a colostomy)

* = hypertension and/or tachycardia occurred when the peritoneum and colon were handled by the surgeon

† = invasively monitored

Anaesthesia was induced by intravenous injections of methohexitone 1 mg kg^{-1} (given in 15 s) and pancuronium 0.1 mg kg^{-1} . The patients were then ventilated by hand using a Magill circuit and face mask with a mixture of oxygen (4 l), nitrous oxide (8 l) and enflurane 0.4%. After 3 min the trachea was intubated. Subsequent anaesthesia consisted of nitrous oxide and oxygen (66%/34%) and enflurane (0.4% inspired) plus intravenous supplements of pancuronium 0.5 mg and diamorphine (our routine preoperative analgesic) 0.5 mg as required. Expired carbon dioxide concentration was continually monitored (capnograph—Godart) and ventilation adjusted to give an end-tidal carbon dioxide concentration of 4.5–5.5%. At the end of the surgical procedure, the enflurane and nitrous oxide were switched off and atropine 1.2 mg and neostigmine 2.5 mg were used to reverse the effects of neuromuscular blockade.

Detailed sensory testing and examination of motor power and co-ordination in the legs were performed within the first half hour post-operatively and at intervals during the next 48 h. Papavertum 0.2 mg kg^{-1} was given intramuscularly as routine medication in our hospital for post-operative pain.

Student's *t*-test for paired data was applied to the data on cardiovascular parameters.

Results

The BP (systolic/diastolic) and heart rates (HR) of all patients are shown in Table 2.

Paired *t*-tests indicate that there were no cardiovascular changes after midazolam (a) or surgical skin incision (c) (see also Figure 1). After intubation of the trachea (b) HR ($P = 0.01$), systolic BP ($P < 0.002$) and diastolic BP ($P < 0.001$) all increased. HR ($P = 0.02$), systolic BP ($P < 0.001$), and diastolic BP ($P < 0.001$) all increased after manipulation of peritoneum or bowel (d). Five patients undergoing intra-abdominal procedures plus one patient who had a colostomy following a right gracilis muscle transplant exhibited hypertension when the peritoneum and colon were handled. Three patients (1, 5 and 9) also began to sweat at this stage and required intravenous diamorphine to reduce these effects. All other patients required no per-operative opioid. Valsalva manoeuvres performed before and 30 min after the subarachnoid injection of midazolam were normal.

Patients were not sedated by the subarachnoid injection of midazolam and no gross disturbances of respiration were seen. No changes in general sensation (light touch, deep pressure,

joint position sense, vibration sense) or abnormalities of motor power and co-ordination were seen either at 30 min after the midazolam injection, or post-operatively.

Dermatomal levels for the change in sensation produced by pin prick or intradermal injection of saline were demonstrated in all patients and are shown in Table 1. These changes occurred 5–10 min after the midazolam injection. In three cases the dermatomal level of change in sensation evoked by the two stimuli was different, and in each case the level for injection of saline was caudal to that for pin prick. It was possible to plot the regression of these levels post-operatively (Table 3); as they receded caudally approximately three dermatomes per day. Pain associated with stimulation of the wound was noted by these patients when the sensory level to pin prick receded below the upper dermatomal level of the wound. Prior to the caudal recession of dermatomal levels below the surgical incision there was a striking absence of pain associated with the *surgical incision*. It was frequently possible in these patients to squeeze the wound post-operatively; the patient was aware of being squeezed and also of the presence of sutures, which were often reported to be tight, but no frank painful sensation was elicited. Discomfort from perineal incisions and urethral catheters was not experienced during the period of the study.

Post-operative pain relief varied with the dermatomal position of the wound and the original level of the sensory blockade, i.e., the higher the level of block and the more caudal the incision, the longer the pain relief (Table 3). Patient 4 felt wound pain at 4 h post-operatively *above* the level of block (T9/T10) but not below it (she had a midline abdominal incision from dermatomes T7–T12); pain in the lower half of her wound was felt as the sensory level demonstrated by pin prick, progressed caudally over the next 24 h (Table 3). No relationship between dose and original sensory level was noted (Table 1).

Those patients who underwent abdominal surgery had post-operative pain which was poorly localised in the abdomen, deeply situated and not related to the surgical incision. We believe this pain to be of visceral origin and these patients required post-operative opiate. The two patients who had leg operations had no post-operative pain requiring analgesia. One patient had a mild headache post-operatively and no patients experienced side effects such as itching, nausea, or vomiting. Normal sensations evoked by painful stimuli applied to the legs returned after 48–72 h. Four patients who were seen 3 months post-

Table 2 Blood pressure (mean $\pm$ s.d.) (systolic/diastolic mmHg) and heart rate (beats min^{-1}) before and after (*) intrathecal injection of midazolam, (b) intubation of the trachea, (c) surgical incision of the skin and (d) surgical handling of the peritoneum and colon

	1		2		3		4		5†		6		7		8†		9	
	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR
before	126(8)	96(5)	162(3)	73(6)	160(3)	81(8)	157(8)	90(5)	123(3)	97(3)	107(3)	96(10)	95(7)	74(4)	138(3)	83(6)	194(4)	58(2)
	79(5)		102(2)		57(11)		82(7)				60(7)		70(0)				61(7)	
(a) after	124(5)	96(2)	153(5)	78(2)	148(3)	85(5)	154(8)	84(3)	123(4)	95(0)	113(2)	92(6)	97(4)	75(0)	135(5)	83(6)	169(11)	59(1)
	78(4)		100(2)		69(2)		83(4)				60(4)		70(0)				56(4)	
before	110(4)	115(1)	155(10)	82(6)	148(3)	99(5)	148(4)	84(1)	123(4)	95(0)	107(2)	87(7)	107(4)	96(2)	108(2)	102(3)	132(10)	73(3)
	69(2)		90(5)		73(3)		85(3)				71(3)		67(4)				56(2)	
(b) after	230(22)	130(7)	190(20)	95(8)	190(8)	131(10)	181(4)	92(3)	160(14)	128(10)	148(13)	112(8)	133(8)	105(4)	135(5)	124(5)	243(8)	101(10)
†	125(12)		110(15)		91(6)		98(3)				102(8)		80(0)				93(8)	
before	176(7)	125(3)	170(8)	85(4)	129(8)	90(5)	133(6)	76(4)	115(7)	105(4)	137(3)	117(11)	112(3)	80(0)	110(0)	120(0)	181(2)	75(1)
	107(4)		90(6)		79(3)		78(3)				87(3)		68(3)				66(2)	
(c) after	167(5)	117(7)	175(6)	88(5)	137(4)	89(4)	128(3)	75(5)	121(2)	105(1)	118(6)	113(7)	110(0)	79(4)	112(3)	117(6)	178(8)	77(1)
	107(5)		92(4)		77(4)		75(0)				73(9)		70(0)				68(4)	
before	167(5)	117(7)	173(5)	82(5)	137(4)	90(4)	128(3)	75(5)	121(2)	105(1)	112(3)	96(2)	112(3)	65(5)	—	—	170(5)	70(2)
	107(5)		90(5)		77(4)		75(0)				70(3)		72(3)				63(3)	
(d) after	194(8)	117(7)	178(4)	87(3)	160(8)	96(5)	154(6)	98(10)	129(7)	106(2)	134(7)	123(3)	127(8)	80(6)	—	—	194(4)	74(2)
**	110(2)		95(4)		91(8)		87(6)				84(4)		80(0)				84(4)	

Readings made every 30 s for 3 min
†diastolic blood pressure not measured
*after = 15 min post injection of midazolam
‡significant rises in HR ($P < 0.01$) systolic BP ($P < 0.002$) and diastolic BP ($P < 0.001$)
**significant rises in HR ($P = 0.02$) systolic BP and diastolic BP ($P < 0.001$)

Figure 1 Sympathetic nervous system mediated responses before and after intrathecal injection of 1.5 mg midazolam in a single patient.

Valsalva manoeuvres (a) and (b) 30 min after intrathecal midazolam. Both responses show the normal features:

- (i) compensatory tachycardia during forced expiration against a closed glottis
- (ii) rebound hypertension upon release
- (iii) reflex bradycardia in response to (b)

(c) no change in blood pressure or heart rate occurred after the spinal injection of midazolam at 1

Induction of anaesthesia at 2

(d) normal hypertensive and tachycardic responses occurred after intubation of the trachea (3) and passage of a nasogastric tube (4)

(e) no cardiovascular changes occurred in response to the surgical skin incision (5) but hypertension was produced by bowel manipulation (6).

Table 3 Dermatomal levels of changes in sensations evoked by sharp pin prick (P) and intradermal injection of saline (I) and post-operative pain in two subjects

	Pre-operatively				Post-operatively					
			4 h		4-12 h		12-24 h		24-48 h	
	a	b	a	b	a	b	a	b	a	b
P	T4	T4	T10	T3	T10	T3	T10	T6	T12	T7
I	T10	T4	—	T5	—	T15	—	—	—	T10
Dermatomal level of wound pain	—	—	T10 ⁰	None†	T10 ⁰	None†	T10 ⁰	None†	T11	T8*
Deep 'visceral' pain	—	—	Yes	None	Yes	None	Yes	None	No	None
Doses of papaveretum (0.2 mg kg ⁻¹) received	—	—	1	0	0	0	1	0	0	0

* Pain felt at colostomy site only at 33 h post-operatively—not enough to require opiate

† No pain produced by pinching of leg wound

⁰ No pain produced by pinching of the wound below T10 but very painful above

(a) Patient 2 had a laparotomy and right hemicolectomy. This involved a midline skin incision involving dermatomes T8–T12

(b) Patient 7 had a right gracilis muscle transplant and a covering transverse colostomy for faecal incontinence. This involved an incision on the medial side of the right leg involving dermatomes L1–L3, a perineal incision S2–S4) and a small abdominal incision (T8) for the colostomy.

operatively for further surgical procedures showed no neurological sequelae and two expressed a preference for this method to a previously experienced local anaesthetic block for post-operative analgesia.

Discussion

Several lines of evidence indicate that sympathetic nervous system function remains intact after intrathecal midazolam. There were no significant changes and normal Valsalva manoeuvres were produced in the 30 min following injection. Cardiovascular responses occurred following intubation of the trachea at a light plane of anaesthesia but no such changes indicated inadequate anaesthesia during surgical incision of the skin. The subsequent cardiovascular responses to incision of the peritoneum and handling of the bowel suggest two things:

- a plane of anaesthesia sufficiently light to allow sympathetic reflex effects to be evoked by noxious stimuli was present during skin incision since no changes in inspired concentration of anaesthetic or ventilatory parameters were made in the intervening period after intubation; these observations act as controls for the subsequent observations of cardiovascular response to the noxious stimulation caused by manipulation of the bowel.
- reflexes evoked by somatic stimulation were interrupted but not those evoked by visceral

stimulation. This could be explained by an inadequately rostral level of blockade. Skin testing indicated an upper thoracic level of blockade—levels normally regarded as sufficient for colonic and pelvic surgery when using local anaesthetics for conduction anaesthesia.

The skin tests indicate the level of blockade of somatic nociceptive afferent pathways in the spinal cord and therefore the level reached by the drug. Reflex effects from visceral nociceptive afferents from the colon and pelvic peritoneum innervated from more caudal spinal cord segments were not affected and this may indicate that spinal cord pathways of somatic and visceral afferents are different. It is generally accepted that the intraspinal pathways for visceral afferent fibres differ from those of somatic afferents (Cervero, 1985). It seems likely that the midazolam did extend far enough rostrally to interrupt visceral afferent pathways, but since the reflexes evoked by these afferents remained intact we could be led to conclude that different neurotransmitter mechanisms are involved.

Our observations are compatible with the findings of Whitwam *et al.* (1982) on somato-sympathetic reflexes in the anaesthetised dog. The two patients (7 and 8) who had operations on the leg and therefore were subjected to somatic painful stimulation only, did not show cardiovascular responses to surgery and required no pre- or post-operative opioids for pain relief. Patient 7 had a colostomy as well as surgery on

the leg; and again the arterial pressure and heart rate rises were caused by manipulation of the colon but not by surgical skin incision. No visceral pain was felt by this patient post-operatively (perhaps because no blood or damaged tissue was present inside the abdomen after such a minor operation); wound pain was not experienced until 48 h post-operatively.

The pattern of early post-operative sensations seems compatible with the observations on visceral and somatic sympathetic reflexes because pain felt by patients was not directly related to the abdominal incision but was rather deep and poorly localised within the abdomen. More work is required to elucidate the pattern of post-operative pain relief with this drug given intrathecally. This particular method of selective sensory blockade poses new problems in the assessment of post-operative pain relief which have been highlighted by the pilot study. We quickly found problems when asking patients to distinguish between a sharp pricking sensation (sensations like this are left intact) and a sharp pricking *painful* sensation. Our patients found it difficult to separate these two qualities of sensation which normally occur together. The occurrence of pain of visceral origin also makes the assessment of pain relief by analogue pain scores and post-operative requirements for opiates, unreliable.

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