ORIGINAL PAPERS

HYPERBARIC OXYGEN DOES NOT DELAY THE ABSORPTION OF INTRAMUSCULAR MIDAZOLAM

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Abstract

AIM: To determine if hyperbaric oxygen at a pressure of 2.8 atmospheres absolute (ATA) (2.8 bar or 18 msw) delays the time to the peak blood level of midazolam given by intramuscular injection.

METHOD: Twenty volunteers were given 0.05 mg/kg of midazolam by intramuscular injection while breathing 100% oxygen at 2.8 bar. Blood was collected every five minutes to determine when the peak blood level occurred. This was then compared with the results when the same group was given the same dose at one atmosphere, breathing air.

RESULTS: In 65% of the subjects, peak blood levels occurred earlier while at 2.8 bar than at 1 bar. In only 15% did peak blood levels occur significantly later at 2.8 bar than at 1 bar. Mean time to peak blood level was 33 minutes at 2.8 bar and 41 minutes at 1 bar.

CONCLUSION: Hyperbaric oxygen at 2.8 bar does not delay the absorption of intramuscular midazolam.

Key words

Drugs, hyperbaric oxygen, treatment.

Introduction

Medications are not given by intramuscular (IM) injection in hyperbaric chambers because it is presumed that vasoconstriction secondary to hyperoxia would delay absorption. Previous studies have confirmed that vasoconstriction does occur under hyperbaric conditions. The effect of this on drug absorption from IM sites is theoretical and has not been tested.

This study was to determine if hyperbaric oxygen at 2.8 atmospheres absolute (ATA or bar) delays the absorption of IM midazolam.

This has clinical applications as IM midazolam is now frequently the first line pharmacological treatment for convulsions. Convulsions in the hyperbaric environment are not infrequent and can be difficult to manage.

Method

Approval was gained from the Fremantle Hospital Ethics Committee. Informed consent was obtained from the 20 volunteers and all were given written information on the aims of the study and potential side effects. The volunteers had to be fit for hyperbaric exposure and over the age of 18. Contraindications to participation included intercurrent illness, not being within 25% of ideal body weight, on other medications and pregnancy.

A 16 gauge intravenous (IV) cannula was placed in an antecubital vein and a baseline 3 ml blood sample taken. Blood was collected in 4 ml lithium heparin plastic tubes. The subject was then compressed to 2.8 bar and 100% oxygen was commenced using a head hood. One minute after commencing oxygen, 0.05 mg/kg midazolam was given by IM injection into the lateral aspect of the right thigh. This dose was chosen to ensure quantifiable serum levels while avoiding deep or prolonged sedation in the subjects. A 5 mg/ml preparation of midazolam was used. Doses ranged between 3 and 5 mg. Further sample collection began ten minutes after the injection and continued every 5 minutes for 60 minutes. After each blood sample was drawn a 3 ml saline flush was given to avoid cannula occlusion. Immediately before taking the next sample 3 ml of blood was withdrawn from the cannula to avoid saline dilution.

The volunteer and an attendant were compressed to 2.8 bar (18 m) for 60 minutes, with 5 minute air breaks after 25 and 55 minutes. Decompression followed the 1992 DCIEM "In Water Oxygen Decompression" tables. Ascent from 18 m to 9 m was over 15 minutes, followed by 5

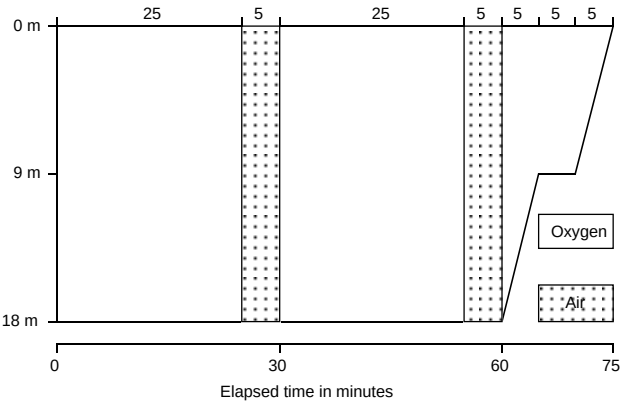

Figure 1. The dive profile used. The numbers across the top are minutes for each segment of the profile. Dotted areas are air breaks. The participants breathed oxygen except when having air breaks. The inside attendant breathed air except during the ascent from 9 m.

minutes at 9 m and then ascent to the surface over a further 15 minutes (Figure 1). The attendant breathed oxygen from 9 m to the surface.

After at least three days the procedure was repeated on the same volunteers who acted as their own control group. This three day break was used to avoid residual midazolam contaminating the base line sample. Days were chosen where the volunteers had experienced a similar level of physical activity to the original sampling. This should have avoided any significant alteration in drug absorption due to variations in baseline muscle blood flow. At no stage was sampling done on volunteers after heavy exercise. Sampling was identical for the control group except that the subjects were kept at 1 bar and were breathing air. All samples were taken by the author.

On completion of each sampling period the subjects were observed for 1 hour and then allowed home under supervision. All were advised not to drive or operate heavy machinery within 6 hours of the injection.

Samples were analysed by high performance liquid chromatography after extraction from alkaline solution into diisopropylether which was taken to dryness. Quantification was effected by comparison with standard additions of midazolam and internal standard blank serum with final analysis by absorption at a wavelength of 254 nm. The correlation coefficient over the range 10 to 100 µg/l was 0.999, with coefficient of variation at 10 and 100 µg/l being 8.4% and 3.3% respectively.

Statistical analysis was performed using the paired T test. Univariate analysis was undertaken to describe the results in each of the two testing periods.

Results

Twenty volunteers were studied. There were 13 men and 7 women. Mean age was 31 years (range 22-46). All volunteers had previous exposure to either diving or hyperbaric chambers. The results are displayed in Table 1.

In 65% (13/20) of the subjects, peak blood levels occurred earlier at 2.8 bar than at 1 bar. In 25% (5/20), peak blood levels were later at 2.8 ATA than at 1 ATA. In 10% (2/20) peak blood levels occurred at the same time at 2.8 and 1 bar. The mean time to peak blood level at 2.8 bar was 33 minutes (95% CI: 28-38). Mean time to peak blood level at 1 bar was 41 minutes (95% CI 35-47). This difference in mean peak times is not statistically significant ($t = -2.0$, $df = 19$, $p=0.060$). In all but 4 of the subjects, an earlier peak time corresponded to a higher peak level.

If the assumption is made that a difference of up to five minutes in the time of achieving peak blood level at the two pressures is not clinically relevant, then 65% (13/20) had their peak earlier at 2.8 bar, 20% (4/20)peaked at the same time in both pressures and only 15% (3/20) peaked later at 2.8 bar than at 1 bar.

TABLE 1

Time to peak level data

Subject	**2.8 bar**		**1 bar**	
	Time minutes	Level µg/ml	Time minutes	Level µg/ml
1	30	32	40	51
2	35	31	55	18
3	35	43	45	41
4	35	54	50	47
5	20	51	30	19
6	30	54	45	38
7	45	47	55	39
8	25	44	55	56
9	10	38	45	26
10	35	59	50	35
11	15	70	60	29
12	35	82	50	60
13	30	58	45	34
14	35	50	35	26
15	30	50	30	52
16	35	18	15	28
17	35	51	30	36
18	35	52	15	73
19	35	34	25	51
20	55	36	50	23

Time to peak blood level of greater than or equal to 45 minutes has previously been used to define delayed absorption.[1] In this study 90% of the 2.8 bar group had peaked by 45 minutes as compared to 60% in the 1 bar group.

No side effects occurred in any of the subjects.

Discussion

Midazolam, 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo benzodiazepine, is used for premedication, sedation and anaesthetic induction. It is also becoming increasingly used as an anticonvulsant after it was shown to be effective in status epilepticus.[1,2] It has a number of advantages over diazepam because of its unique physiochemical properties. At a pH of 4, the diazepine ring of midazolam opens producing a highly water soluble compound. Consequently it is available without the need for organic solvents such as propylene glycol which can cause venous irritation and cardiac arrhythmias. At a pH of greater than 4, the ring closes, resulting in increased lipophilicity and, consequently, its fast onset of action.[3] Unlike diazepam it is rapidly absorbed following IM

injection with a bioavailability of 90%.[4] Onset of sedation is rapid and previous studies have shown mean peak blood levels at 20-25 minutes but with considerable individual variation.[4,5] Central nervous system effects of midazolam follow the blood levels closely.[6] It is metabolised by the cytochrome P450 system to several metabolites including the active alpha-hydroxymidazolam. The elimination half-life of 1.5-3 hours is short compared with more than 20 hours for diazepam.[7] Alpha hydroxymidazolam has an elimination half-life of 1 hour.[8]

Hyperbaric medicine staff should be familiar with the use of midazolam because there are multiple causes of potential convulsions in the hyperbaric chamber. Common causes include cerebral oxygen toxicity, pre-existing epilepsy and cerebral irritation from decompression illness or carbon monoxide poisoning. Convulsions from cerebral oxygen toxicity are generally self limiting once the oxygen is ceased. Convulsions secondary to the other causes, however, can be prolonged requiring treatment along standard emergency guidelines.

Intravenous midazolam or diazepam are the first line pharmacological agents in the treatment of convulsions. However not all patients in a hyperbaric chamber will have an intravenous cannula in place. Midazolam given IM is now the preferred first line treatment for convulsions in many Australian emergency departments. Its use enables the insertion of an intravenous line for ongoing treatment under easier conditions. Intravenous lines are difficult to insert in a convulsing patient and there will also be a time delay if a doctor is required to lock into the chamber to place the line. Intramuscular midazolam has been shown to be effective in stopping prolonged seizures in children and adults. In the study by McDonagh et al. only 5% failed to respond.[2] Seizures were terminated in 1 minute 53 seconds on average (range 15 seconds to 6 minutes 7 seconds). Epileptiform activity has also been shown to either disappear or be significantly reduced after IM administration.[9] Midazolam is more effective than IM diazepam and as effective as IV diazepam 5 minutes after injection.[10,11] Intramuscular diazepam is absorbed both slowly and erratically and the peak blood concentration does not occur until 60 minutes.[12] Rectal absorption of midazolam has been shown to be poor and irregular.[13]

Medications are not usually given by the intramuscular route in hyperbaric chambers because hyperoxia results in vasoconstriction. This has been shown in skeletal muscle,[14] the brain,[15] retina,[16] and abdominal organs.[17] The vasoconstriction has been presumed to delay the absorption of the intramuscular medication. Potential problems of delay in absorption include failure of the drug to reach a therapeutic concentration and also the release of a bolus of drug once hyperbaric exposure ends and vasoconstriction ceases. Although vasoconstriction has definitely been shown to occur, the effects of this on drug absorption from the intramuscular site have never been reported. This study suggests that absorption of intramuscular midazolam is significantly delayed in only 15% at 2.8 bar compared to 1 bar and that the mean time to peak blood level is shorter at 2.8 bar. Although statistical significance has not been reached due to a lack of power (0.15), the hypothesis that hyperbaric oxygen delays the absorption of intramuscular midazolam is not supported.

Intramuscular midazolam could therefore be a safe and effective treatment for patients with prolonged convulsions in hyperbaric chambers. Because of the unique pharmacology of midazolam this recommendation cannot be extended to all medications under pressure. However, the situation of a prolonged convulsion in a patient under pressure would be the main circumstance where it would be useful to be able to give IM medications. In the small percentage of patients whose convulsion does not respond to IM midazolam after 3 minutes then IV access can be obtained and treatment with IV midazolam instituted as would occur under normal emergency medicine practice.

One of the limitations of the study is that, although vasoconstriction occurs, no studies have addressed when it begins. Measurements in most of the studies begin at 15 minutes and have confirmed vasoconstriction at that stage. Theoretically a considerable amount of midazolam may have been absorbed before vasoconstriction occurred. However, vasoconstriction is a reflex precipitated by hyperoxia and would be expected to occur immediately the tissues become hyperoxic. Additionally, one study has found that in patients with traumatic cerebral oedema treated with hyperbaric oxygen, intracranial pressure (ICP) decreased as soon as treatment pressure was reached.[18] Reduction in ICP is attributed to vasoconstriction of cerebral arteries.

The dose of midazolam used was subtherapeutic but this should not have affected the time to peak blood level. Increasing the dose increases the peak blood level but the time to the peak is determined by the volume of distribution and the rate of drug absorption from muscle. Volume of distribution of midazolam is neither age nor sex related but obesity increases it.[19] In this study all subjects were within 25% of their ideal body weight. The rate of drug absorption from muscle is determined by blood flow to the site and the physiochemical properties of the drug. Variation in blood flow to the site was minimised by controlling for physical activity prior to testing, testing at the same time of day and using the same site for injection.

Conclusion

Hyperbaric oxygen at 2.8 ATA does not delay the absorption of IM midazolam. This suggests that IM midazolam may be a safe and effective treatment for prolonged convulsions in patients in hyperbaric chambers who do not have intravenous access already established. There is a need for further studies in a clinical setting.

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References

1 Jelinek GA and Galvin GM. Midazolam in status epilepticus in children. *Crit Care Med* 1994; 22 (8): 1340-1341
2 McDonagh TJ, Jelinek GA and Galvin GM. Intramuscular midazolam rapidly terminates seizures in children and adults. *Emerg Med* 1992; 4: 77-81
3 Pieri L et al. Pharmacology of midazolam. *Arzneim.-Forsch* 1981; 31: 2180-2201
4 Bell DM et al. A comparative pharmacokinetic study of intravenous and intramuscular midazolam in patients with epilepsy. *Epilepsy Res* 1991; 10: 183-190
5 Alfonzo-Echeverri E, Troutman KC and George W. Absorption and elimination of midazolam by submucosal and intramuscular routes. *Anaesth Prog* 1990; 37: 277-281
6 Crevoisier C, Zeigler WH, Eckart M and Heijmann P. Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. *Br J Clin Pharmacol* 1983; 16: 51-61
7 Stanski DR and Hudson RJ. Midazolam pharmacology and pharmacokinetics. *Anesth Rev* 1985; 12: 21-23
8 Kanto JH. Midazolam: the first water-soluble benzodiazepine, pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 1985; 5: 138-155
9 Ghilan S, Van Rijckevorsel-Harmant S and Harmant J. Midazolam in the treatment of epileptic seizures. *J Neurol Neurosurg Psychiatry* 1988; 51: 732
10 Raines A, Henderson TR, Swinyard EA and Dretchen KL. Comparison of midazolam and diazepam by the intramuscular route for the control of seizures in a mouse model of status epilepticus. *Epilepsia* 1990; 31(3): 313-317
11 Jawad S, Oxley J, Wilson J and Richens A. A pharmacodynamic evaluation of midazolam as an antiepileptic compound. *J Neurol Neurosurg Psychiatry* 1986; 49: 1050-1054
12 Barsan WG, Ward JT Jr. and Otten EJ. Blood levels of diazepam after endotracheal administration in dogs. *Ann Emerg Med* 1982; 11: 242-247
13 Payne K, Mattheyse FJ, Liebenberg D and Dawes T. The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989; 37: 267-272
14 Dooley JW and Mehm WJ. Noninvasive assessment of the vasoconstrictive effects of hyperoxygenation. *J Hyperbaric Med* 1990; 4(4): 177-187
15 Kety SS and Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J Clin Invest* 1948; 27: 484-492
16 Dollery CT, Hill DW, Mailer CM and Ramalho PS. High oxygen pressure and the retinal blood vessels. *Lancet* 1964; 11: 291-292
17 Hordnes C and Tyssebotn I. Effect of high ambient pressure and oxygen tension on organ blood flow in conscious trained rats *Undersea Biomed Res* 1985; 12(2): 115-128
18 Sukoff MH and Ragatz RE. Hyperbaric oxygenation for the treatment of acute cerebral oedema. *Neurosurgery* 1982; 10(1): 29-38
19 Greenblatt DJ, Abernethy DR, Lochniskar A, Harmatz J, Limjuco RA and Shader RI. Effects of age, gender and obesity on midazolam kinetics. *Anesthesiology* 1984; 61: 27-35

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SHARPENING THE SHARPENED ROMBERG

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Key Words

Decompression illness, investigations, treatment.

Abstract

The Sharpened Romberg Test (SRT) is a test of balance commonly used in Diving Medicine. Interpretation of an abnormal test can be confounded by