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COMPARISON BETWEEN MIDAZOLAM AND THIOPENTONE-BASED BALANCED ANAESTHESIA FOR DAY-CASE SURGERY

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SUMMARY

In a randomized study of 100 women (ASA 1–2) undergoing termination of pregnancy as outpatients, the combination of midazolam–fentanyl–nitrous oxide was compared with thiopentone–fentanyl–nitrous oxide. The induction time (the time recorded until disappearance of the palpebral reflex) was significantly longer in the midazolam group (40 s) than in the thiopentone group (31 s). There were no significant differences in heart rate or arterial pressure between the two groups. Thirty minutes after the termination of surgery the degree of awareness, estimated by means of Glasgow Coma Scale, was lower in the midazolam group. After 60 and 180 min the scores were equal. During recovery more patients experienced side-effects in the thiopentone group than in the midazolam group, the difference being statistically significant 72 h after discharge when 66% and 34% of the patients complained of side-effects, respectively. Midazolam is as suitable as thiopentone for the induction of anaesthesia in day-case surgery.

Midazolam, a water-soluble benzodiazepine with a rapid onset, and relatively short duration of action, has proved to be a satisfactory alternative to thiopentone for the induction of anaesthesia (Conner et al., 1978; Fragen, Gahl and Caldwell, 1978; Reves et al., 1979). Unwanted side-effects are infrequent (Reves et al., 1979; Fragen and Caldwell, 1981), anterograde amnesia is present (Dundee and Wilson, 1980), and patient preference grades have been high when midazolam has been compared with thiopentone (Reves et al., 1979).

Recovery following midazolam-based anaesthesia (midazolam–nitrous oxide–fentanyl) for short gynaecological operations was similar to that following the combination of thiopentone, nitrous oxide and fentanyl (Fragen and Caldwell, 1981) and the authors concluded that "midazolam could be useful for outpatient anaesthesia if 4 h elapse before patients are discharged".

The aim of the present investigation was to determine the feasibility of the combination of midazolam, nitrous oxide and fentanyl for this purpose.

PATIENTS AND METHODS

One hundred women (ASA 1–2) with a pregnancy of less than 12 weeks duration and scheduled for termination of pregnancy (TOP) on an outpatient basis were allocated randomly to one of two groups (A and B).

The trial was conducted in accordance with the Helsinki II Declaration and with the approval of the County Ethics Committee. Informed consent was obtained from each patient. Patients were excluded from the study on account of myasthenia gravis, recorded allergy to benzodiazepines, known abuse of alcohol or sedatives, or previous thromboembolic disorders.

Premedication consisted of droperidol 5 mg i.m. 30 min before surgery.

In group A ($n = 50$), anaesthesia was induced with midazolam 0.2 mg kg^{-1} i.v. injected over 30 s. A further injection of midazolam 0.1 mg kg^{-1} was administered if the eyelash reflex was present 3 min after the initial dose. Immediately after loss of consciousness, fentanyl 0.15 mg was administered i.v. and anaesthesia was maintained with 67% nitrous oxide in oxygen. If necessary (in response to movement, peripheral vasoconstriction, lachrymation, sweating, alteration in heart rate or arterial pressure), supplementary doses of midazolam 0.15 mg kg^{-1} or fentanyl 0.10 mg, or both, could be administered.

In group B ($n = 50$), anaesthesia was induced with thiopentone 4 mg kg^{-1} i.v. A supplementary dose (2 mg kg^{-1}) was given if required after 3 min. Following fentanyl 0.15 mg i.v., anaesthesia was maintained with 67% nitrous oxide in oxygen combined with supplementary doses of thiopentone 3 mg kg^{-1} or fentanyl 0.10 mg, or both.

After surgery, the patients were transferred to a

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recovery unit where they were observed for 2 h. All patients were discharged from hospital 6 h after surgery.

The induction interval (the total time to loss of the eyelash reflex), the duration of anaesthesia and the blood loss were recorded. Arterial pressure (AP) and heart rate were recorded every 5 min. Following termination of anaesthesia, the total requirements for midazolam, thiopentone and fentanyl were calculated.

In the recovery unit, arterial blood–gas tensions were measured 1 h after the termination of anaesthesia and the respiratory rate was measured every 15 min. The degree of awareness was assessed by means of the Glasgow Coma Scale 30, 60, and 180 min after termination of anaesthesia (Teasdale and Jennett, 1974). This scale was considered appropriate as it is one of the few scales for estimating the general functional condition of the cerebrum, that is, equivalent of a direct assessment of the degree of sedation, by means of determining the level of consciousness on the basis of eye reactions, verbal and other motor reactions. Estimation of the motor function was modified to minimize various degrees of influence on the brain stem. Minimum and maximum of the scale are 0 and 10 points, respectively.

Before leaving the recovery unit, the patients were interviewed and unwanted side-effects, such as nausea, vomiting and dizziness, were recorded, in addition to the degree of amnesia.

On discharge, patients were handed a questionnaire, to be returned 72 h later, requesting information on specified complaints in regard to anaesthesia and the recovery period. The final question was whether or not the same type of anaesthesia would be acceptable on a future occasion.

TABLE I. *Details of patients, induction time and duration of anaesthesia. Median (range).* *P <0.01

	Midazolam	Thiopentone
Age (yr)	27 (17–40)	25 (15–42)
Weight (kg)	58 (35–92)	60 (48–79)
Weeks of pregnancy	8 (6–11)	8 (5–11)
Induction time (s)	40* (15–105)	31* (15–90)
Duration of anaesthesia (min)	20 (5–41)	20 (11–36)

The results were analysed for statistical significance ($P<0.05$) using paired Student's t test and Pratt test for within group comparisons and χ^2-test and Mann–Whitney Rank Sum tests for unpaired data for group comparisons.

RESULTS

There were no significant differences between the two groups in age, weight, arterial pressure, heart rate and blood loss ($P>0.10$ in each case).

The induction time (table I) was significantly longer for midazolam than for thiopentone, the median values being 40 and 31 s, respectively. It was not necessary to administer further injections to induce anaesthesia in any of the patients in either group.

Significantly more patients required maintenance doses of thiopentone than of midazolam (43 (86%) compared with 17 (34%) ($P<0.0005$)). The median number of maintenance doses of thiopentone (1.3, range 0–4) was significantly higher than the median number of maintenance doses of midazolam (0.4, range 0–2) ($P<0.001$) (table II).

The median consumption of fentanyl was equal in both groups (0.15 mg).

A lower degree of consciousness, shown by a lower score in the Glasgow Coma Scale, was found 30 min after termination of anaesthesia with midazolam compared with thiopentone. However, by 60 min there was no longer any significant difference between the two groups (table III).

Arterial blood-gas tensions, determined 1 h after surgery, were found to be normal and there were no significant differences between the two groups.

Retrograde amnesia was found in one patient in the midazolam group and in two who received thiopentone, as they did not recall their arrival in the operating theatre. No patient was able to remember any part of the operation. In group A, the duration

TABLE II. *Medication. Median (range).* *P <0.001

	Midazolam	Thiopentone
Induction agent (in total) (mg)	14.8 (10–22.5)	350 (250–550)
Induction agent (induction dose) (mg)	12.5 (7.5–20)	250 (200–400)
Induction agent (maintenance dose) (mg)	5.1 (2.5–10)	100 (50–300)
Induction agent (number of maintenance doses)	0.4* (0–2)	1.3* (0–4)

TABLE III. *Glasgow Coma Scale score for awareness during recovery. Maximum possible score: 10 points. Median (95% interpercentile range).* *P < *0.01*

	Midazolam	Thiopentone
After 30 min	9.4* (5.1–10.0)	9.7* (8.5–10.0)
After 60 min	9.7 (8.5–10.0)	9.7 (9.1–10.0)
After 180 min	10.0	10.0

of anterograde amnesia was 30 min (median value, range 15–60 min), and in group B, 30 min (median value, range 5–60 min).

No patients required analgesic administration during recovery. Unwanted side-effects are illustrated in table IV. More patients in the thiopentone group recollected unpleasant symptoms during recovery when rating these 72 h after discharge from hospital (66% compared with 34%) ($P < 0.005$).

Four women in group A (midazolam) and seven in group B (thiopentone) required antiemetic medication during recovery (metoclopramide 10 mg). When estimating the degree of discomfort during induction of anaesthesia, and recovery, the percentage of the patients who had experienced no discomfort at all appeared to be 72%/90% for midazolam and 70%/90% for thiopentone.

Most patients in both groups were satisfied with their anaesthetic: 82% after midazolam and 78% after thiopentone.

DISCUSSION

The choice of anaesthesia for outpatient procedures has always been controversial. In 1972, Lennartz claimed that the technique of anaesthesia must be based on the duration of surgery. Monheim (1973) believed that any anaesthetic combination for outpatients must produce a level of consciousness sufficiently low to cause disinterest in surroundings as well as analgesia.

Midazolam, when compared with diazepam, has a shorter induction time (Reves, Corssen and Holcomb, 1978; Sarnquist et al., 1980), a shorter duration of action (Brown, Sarnquist and Pedley, 1977; Sarnquist et al., 1980), and forms water-soluble salts making it less liable to cause venous complications (Fragen, Gahl and Caldwell, 1978; Reves, Corssen and Holcomb, 1978; Sarnquist et al., 1980; Jensen, Hüttel and Schou Olesen, 1981.)

Not unexpectedly, the induction time with midazolam appeared to be longer than with thiopentone. This may be explained by the higher lipid solubility of the latter (Sarnquist et al., 1980). However, the median values for midazolam in this trial were shorter than those recorded in similar trials (Fragen, Gahl and Caldwell, 1978; Reves, Corssen and Holcomb, 1978; Fragen and Caldwell, 1981).

In accordance with the great variability in

TABLE IV. *Number of patients with side-effects during the recovery period and the days after surgery (% of patients)* *P < *0.025*; **P < *0.005*

	Midazolam			Thiopentone		
	During recovery period		During days after the operation	During recovery period		During days after the operation
	Rated by nurse	Rated by patient	Rated by patient	Rated by nurse	Rated by patient	Rated by patient
Nausea	9 (18%)	2 (4%)*	2 (4%)	13 (26%)	10 (20%)*	5 (10%)
Vomiting	4 (8%)	3 (6%)	1 (2%)	8 (16%)	9 (18%)	0 (0%)
Dizziness	3 (6%)	13 (26%)	10 (20%)	7 (14%)	18 (36%)	9 (18%)
Visual disturbances		1 (2%)	1 (2%)		5 (10%)	4 (8%)
Anxiety		2 (4%)	2 (4%)		3 (6%)	1 (2%)
Temperature			4 (8%)			1 (2%)
Tiredness			21 (42%)			29 (58%)
Respiratory depression	0 (0%)			0 (0%)		
Headache		1 (2%)			5 (10%)	
Total no. with side-effects	11 (22%)	17 (34%)**	25 (50%)	19 (38%)	33 (66%)**	32 (64%)

dose–responses with benzodiazepines, the range of induction times in the midazolam group was wide but, surprisingly, this was also the case in the thiopentone group (Reves, Corssen and Holcomb, 1978). Sarnquist, Mathers and Brown (1978) calculated the potency of midazolam to be 20 times that of thiopentone—a ratio consistent with our results.

Maintenance of anaesthesia was smoother in the midazolam group as demonstrated by the greater requirement for maintenance doses in the thiopentone group. Reves, Corssen and Holcomb (1978) reached the same conclusion with shorter surgical procedures, whereas Fragen and Caldwell (1981) recorded an equal number of maintenance doses with the two agents. In 1970, Wyant and Studney demonstrated the superiority of diazepam over thiopentone for maintenance of anaesthesia.

Alterations of arterial pressure and heart rate were similar to the observations of other authors (Brown et al., 1978; Reves, Corssen and Holcomb, 1978; Sarnquist, Mathers and Brown, 1979; Sarnquist et al., 1980).

Recovery was slower after midazolam anaesthesia, but there were fewer unwanted side-effects than with thiopentone. Midazolam is distributed rapidly following injection i.v., but is also metabolized rapidly and eliminated without active metabolites (Nagai, Tseng and Wang, 1966; Amrein et al., 1981; Crevoisier et al., 1981; Pieri et al., 1981; Ziegler et al., 1981). The differences of plasma half-life of the two agents presumably explain the variations in length of recovery, the reported values being 46–48 min for thiopentone (Ghoneim and Van Hamme, 1977) and 102 min for midazolam (Puglisi et al., 1978). Anterograde amnesia is a well-known quality of the benzodiazepines (Dundee and Haslett, 1970; Greenblatt and Shader, 1974). No difference between midazolam and thiopentone was found in this trial. The three instances of retrograde amnesia (one midazolam and two thiopentone) were probably caused by the amnesic effect of the premedication. Olsen (1976), using a thiopentone–fentanyl anaesthetic technique in a group of patients similar to those in the present study observed nausea and vomiting in 20% and 10% of patients during the first 24 h after surgery. Although these adverse effects were the most frequent complaints in the midazolam group in the present study, they were of shorter duration than in the thiopentone group, an observation previously made by Fragen and Caldwell (1981). No instance of delayed sedation was observed.

Under the conditions of the present study midazolam is a suitable agent for the induction of anaesthesia for day-case surgery and, in many respects, particularly the lower frequency of unwanted side-effects, it is superior to a thiopentone-based technique.

REFERENCES

Amrein, R., Cano, J. P., Eckert, M., and Coassalo, P. (1981). Pharmacokinetics of midazolam after i.v. administration. *Arzneim.-Forsch./Drug. Res.*, **31**, 2202.

Brown, C. R., Sarnquist, F. H., Mathers, W. D., Brock-Utne, J. G., Canup, C. A., and Carr, B. L. (1978). Clinical comparison of midazolam maleate with thiopental as anesthetic induction agents. *Annual Meeting Am. Soc. Anesth.*, 421.

——— Pedley, T. A. (1977). Ro 21-3981: clinical, electroencephalographic and pharmacokinetic study. *Annual Meeting Am. Soc. Anesth.*, 241.

Conner, J. T., Katz, R. L., Pagano, R. R., and Graham, C. W. (1978). Ro 21-3981 for intravenous surgical premedication and induction of anesthesia. *Anesth. Analg.*, **57**, 1.

Crevoisier, P. C., Eckert, M., Heizmann, P., Thurneysen, D. J., and Ziegler, W. H. (1981). Relation between the clinical effect and the pharmacokinetics of midazolam following i.m. and i.v. administration. 2: Pharmacokinetical aspects. *Arzneim.-Forsch./Drug Res.* **31**, 2211.

Dundee, J. W., and Haslett, W. H. K. (1970). The benzodiazepines, a review of their actions and uses relative to anaesthetic practice. *Br. J. Anaesth.*, **40**, 217.

——— Wilson, D. B. (1980). Amnesic action of midazolam. *Anaesthesia*, **35**, 459.

Fragen, R. J., and Caldwell, N. J. (1981). Awakening characteristics following induction with midazolam for short surgical procedures. *Arzneim.-Forsch./Drug Res.*, **31**, 2261.

——— Gahl, F., and Caldwell, N. J. (1978). A water soluble benzodiazepine, Ro 21-3981, for induction of anesthesia. *Anesthesiology*, **49**, 41.

Ghoneim, M. M., and Van Hamme, M. J. (1977). Pharmacokinetics of thiopental: the effects of enflurane and nitrous oxide anesthesia and surgery. *Annual Meeting Am. Soc. Anesth.*, 425.

Greenblatt, D. J., and Shader, R. I. (1974). *Benzodiazepines in Clinical Practice*, p. 204. New York: Raven Press.

Jensen, S., Hüttel, M. S., and Schou Olesen, A. (1981). Venous complications after i.v. administration of Diazemuls (diazepam) and Dormicum (midazolam). *Br. J. Anaesth.*, **53**, 1083.

Lennartz, H. (1972). Outpatient anaesthesia. *Chirurg.*, **43**, 15.

Monheim, L. M. (1973). Monitoring in anaesthesia. *Outpatient Proc.*, **19**, 291.

Nagai, S. H., Tseng, D. S. C., and Wang, S. C. (1966). Effects of diazepam and other central nervous system depressants on spinal reflexes in cats: a study of site of action. *J. Pharmacol. Exp. Ther.*, **153**, 344.

Olsen, P. P. (1976). Outpatient anaesthesia for termination of pregnancy. *Ugeskr. Laeg.*, **138**, 1814.

Pieri, L., Schaffner, R., Scherschlicht, R., Polc, P., Sepinwall, J., Davidson, A., Mohler, H., Cumin, R., Da Prada, M., Burkard, W. P., Keller, H. H., Muller, R. K. M., Gerold, M., Pieri, M., Cook, L., and Haefely, W. (1981). Pharmacology of

midazolam. *Arzneim. Forsch./Drug Res.*, 31, 2180.

Puglisi, C. V., Meyer, J. C., D'arconte, L., Brooks, M. A., and De Silva, J. A. F. (1978). Determination of water soluble imidazo-1,-4,-benzodiazepines in blood by electron-capture gas–liquid chromatography and in urine by differential pulse polarography. *J. Chromatogr.*, 145, 81.

Reves, J. G., Corssen, G., and Holcomb, C. (1978). Comparison of two benzodiazepines for anaesthesia induction: midazolam and diazepam. *Can. Anaesth. Soc. J.*, 3, 211.

—— Vinik, R., Hirschfield, A. M., Holcomb, C., and Strong, S. (1979). Midazolam compared with thiopentone as a hypnotic component in balanced anaesthesia: a randomized, double-blind study. *Can. Anaesth. Soc. J.*, 26, 42.

Sarnquist, F. H., Mathers, W. D., Brock-Utne, J., Carr, B., Canup, C., and Brown, C. R. (1980). A bioassay of a water soluble benzodiazepine against sodium thiopental. *Anesthesiology*, 52, 149.

—— —— Brown, C. R. (1978). Midazolam maleate, a bioassay. *Clin. Pharmacol. Ther.*, 25, 247.

Teasdale, G., and Jennett, B. (1974). Assessment of coma and impaired consciousness. *Lancet*, 2, 81.

Wyant, G. M., and Studney, L. J. (1970). A study of diazepam (valium) for induction of anaesthesia. *Can. Anaesth. Soc. J.*, 17, 166.

Ziegler, W. H., Thurneysen, J. D., Eckert, M., Amrein, R., and Dubuis, R. (1981). Relationship between clinical effects and pharmacokinetics of midazolam on i.m. and i.v. application to volunteers. 1: clinical aspects. *Arzneim.-Forsch./Drug Res.*, 31, 2206.

COMPARAISON ENTRE MIDAZOLAM ET THIOPENTAL POUR L'ANESTHESIE GENERALE BALANCEE AMBULATOIRE

RESUME

Dans une étude randomisée, chez 100 femmes (ASA classe 1 et 2), subissant une interruption de grossesse en ambulatoire, l'association midazolam – fentanyl – protoxyde d'azote a été comparée à l'association thiopental – fentanyl – protoxyde d'azote. Le délai d'induction (durée entre l'injection et la disparition du réflexe palpébral) était significativement plus long dans le groupe midazolam (40 s) que dans le groupe thiopental (31 s). Il n'y avait pas de différence significative de fréquence cardiaque ou de pression artérielle entre les deux groupes. Trente minutes après la fin de l'acte chirurgical, le degré d'éveil, mesuré grâce à l'échelle des comas de Glasgow, était plutôt moins bon dans le groupe midazolam. Au bout de 60 et 180 m, les résultats étaient identiques. Au cours du réveil, plus de patientes ont subi des effets secondaires dans le groupe thiopental que dans le groupe midazolam avec une différence statistiquement significative, 72 h après la sortie, où 66% et 34% respectivement de patientes se plaignaient de tels effets. Le midazolam convient aussi bien que le thiopental à l'induction de l'anesthésie en chirurgie ambulatoire.

COMPARACION ENTRE LA ANESTESIA BASADA EN TIOPENTONA Y EN MIDAZOLAN PARA CIRUJIA EN PACIENTES EXTERNOS

SUMARIO

En un estudio al azar sobre 100 mujeres (ASA 1-2) sometidas a interrupción del embarazo como pacientes externas, se llevó a cabo una comparación de una combinación de midazolán–fentanilo–óxido nitroso con una de tiopentona–fentanilo–óxido nitroso. El tiempo de inducción (el tiempo registrado hasta la desaparición del reflejo palpebral) fue mucho más largo en el grupo con midazolán (40 s) que en el grupo con tiopentona (31 s). No hubo diferencias significativas en el ritmo cardiaco o la presión arterial entre los dos grupos. Treinta minutos después del fin de la cirujía, el grado de consciencia, estimado mediante la Escala de Coma de Glasgow, era algo más bajo en el grupo con midazolán. A los 60 y 180 minutos, las cifras registradas eran iguales. Durante la recuperación, hubo más pacientes con efectos secundarios en el grupo con tiopentona que en el grupo con midazolán, la diferencia siendo más significativa desde el punto de vista estadístico unas 72 horas después cuando un 66% y un 34% de las pacientes se quejaron de efectos secundarios, respectivamente. El midazolán es tan adeccuado para la inducción de anestesia en pacientes externos como la tiopentona.