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EFFECTS OF PREMEDICATION ON DIPRIVAN INDUCTION

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SUMMARY

The effects of three premedication regimens were compared in 45 healthy patients in whom anaesthesia was induced with diprivan 2 mg kg^{-1} I.V. Premedication with diazepam 10 mg orally and droperidol 2.5–5.0 mg and piritramide 7.5–15.0 mg i.m. resulted in less pain on injection and a more profound sleep from diprivan than premedication with diazepam 10 mg orally or no premedication. No differences in speed of induction were found when cessation of counting was used as a sign of unconsciousness. When the loss of eyelash reflex was used to define unconsciousness, the oral and i.m. premedication provided quicker induction after diprivan (39.3 ± 2.9 s) than no premedication (53.7 ± 3.0 s) ($P < 0.05$) with no greater frequency of side-effects. Dose and rate of injection are the two most important factors influencing speed of induction.

Diprivan, ICI 35 868, a phenolic compound with the chemical structure 2,6-di-isopropyl phenol, has been used to induce anaesthesia i.v. (Kay and Rolly, 1977a, b; Kay and Stephenson, 1980; Rolly, Versichelen and Zubair, 1980; Rutter et al., 1980). Diprivan is dissolved in 16% cremophor EL and provided as a 1% solution. A dose of 2 mg kg^{-1} is recommended for induction in unpremedicated patients (Briggs, Dundee and Clarke, 1981). The short duration of action is apparently caused by redistribution and rapid metabolism and the drug can be given by repeated injection or continuous infusion without cumulation (Adam, Glen and Hoyle, 1980; Kay and Adam, 1981). Induction time may be dependent on dose and speed of injection (Kay and Stephenson, 1980), a rapid injection time being advantageous. Because studies with the current formulation have been performed mainly on unpremedicated patients, we examined the effects of premedication on speed of induction and frequency of side-effects.

METHODS

Forty-five healthy adults were studied after giving verbal consent at the time of the preoperative visit. They underwent elective surgery, did not abuse drugs or alcohol, had not recently been exposed to cremophor, had no history of atopy or allergy, and were not pregnant or nursing women. They were randomly assigned to one of three groups to receive no premedication (Group A), diazepam 10 mg orally (group B) or diazepam 10 mg orally plus droperidol 2.5–5.0 mg and piritramide 7.5–15 mg i.m. (group C) 60–90 min before induction of anaesthesia.

An i.v. infusion was inserted to a vein of the hand or forearm and arterial pressure, heart rate and respiratory rate were measured and recorded. Induction of anaesthesia was accomplished with diprivan 2 mg kg^{-1} injected i.v. over 20 s. Patients began counting at the onset of injection and induction time was defined as the time which elapsed from the start of injection until cessation of counting. The time from the start of injection until the eyelash reflex disappeared was also measured. At the end of each minute for the next 3 min, arterial pressure, heart rate and respiratory rate were measured. Mean arterial pressure (m.a.p.) was calculated by the formula: (diastolic pressure + pulse pressure)/3. If apnoea occurred, its duration was recorded. Thereafter, conventional anaesthetics and myoneural blockers were administered. Any side-effects were recorded. If no spontaneous complaint of pain on injection occurred, patients were asked if they had pain, and, if so, where.

Comparisons of all measurements were analysed by a one-way analysis of variance except frequency of apnoea and pain on injection which were analysed by the Chi-square test (Runyon and Haber, 1977). Differences were considered significant when $P < 0.05$.

RESULTS

There were 10 females and five males in each group. A dose of diprivan 2 mg kg^{-1} produced uncon-

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sciousness in all patients. Table I shows the ages, weights, induction times, frequency and duration of apnoea and frequency of pain on injection. The only significant difference between the groups occurred in the time from the start of injection until loss of the eyelash reflex, with a shorter time for patients in group C compared with those who had no premedication. There was a trend to a longer duration of apnoea as the amount of premedication increased. There was also a lesser frequency of pain on injection (20%) in the group receiving a narcotic for premedication, and all patients in this group who experienced pain had the infusion to the back of the hand. The back of the hand was the infusion site for two of seven who had pain on injection and no premedication, and seven of nine who had pain and received only diazepam. The overall frequency of pain on injection was 42%, but in the groups not receiving a narcotic it was 53%. Spontaneous complaints of pain were offered by four patients who received no premedication, seven who received only diazepam and only one who received a narcotic. The other complaints of pain were elicited by questioning the patient after the injection was completed.

Eight of the group who had no premedication and six of the group who had only diazepam (47% of both groups) began to waken before the end of the 3-min period of observation. Awakening did not occur in group C.

Significant changes in mean arterial pressure (m.a.p.) occurred within groups. M.a.p. decreased from control at each of the three subsequent observations in the group with no premedication and at 2 and 3 min after injection in group C. The only significant differences between groups (fig. 1) were for m.a.p. recorded at 2 and 3 min, which was less in group C than in the group which received no premedication. There were no significant changes in heart rate from control in any group. Heart rates recorded at 1 min were significantly less than control in group C.

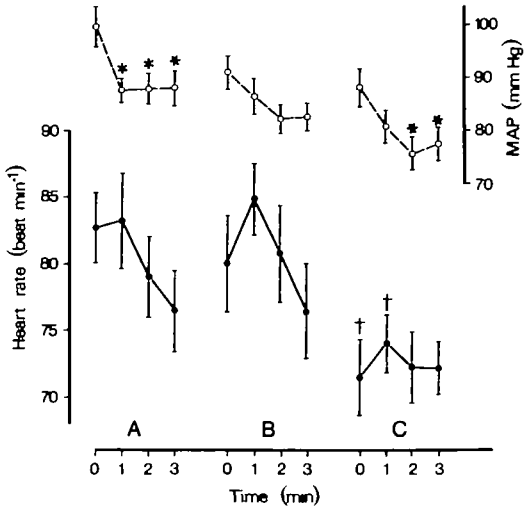

FIG. 1. Mean ± SEM for heart rate and mean arterial pressure (MAP) at control (0) and 1, 2, and 3 min after injection of diprivan. Group A received no premedication, group B diazepam 10 mg orally, and group C diazepam 10 mg orally plus droperidol 2.5–5.0 mg and piritramide 7.5–15.0 mg i.m. †$P<0.05$ *v.* the same time in groups A and B. *$P<0.05$ *v.* control. All other comparisons within the group or between groups are not significant ($P>0.05$).

DISCUSSION

Premedication had no influence on the speed of induction when defined as time to cessation of counting. The mean times of 33.0–39.7 s are comparable to those reported by Major and others

TABLE I. *Demographic data and effects of premedication.* *P< *0.05 compared with no premedication. All other comparisons are not statistically significant. Except for the frequency of apnoea and pain on injection, all values shown are mean ± SEM*

	Type of premedication		
	None	Diazepam 10 mg	Diazepam 10 mg + droperidol 2.5–5.0 mg + piritramide 7.5–15 mg
Age (yr)	32 3±2.7	34.1±2.4	34.5± 4.4
Weight (kg)	71.5±2.9	72.2±4.0	63.7± 2.0
Stop counting (s)	39.7±2.4	33.0±1.8	35.0± 2.1
Loss of eyelash reflex (s)	53.7±3.0	47.7±2.2	39.3± 2.9*
Apnoea (frequency, %)	80	80	100
Apnoea (duration, s)	55.0±5.6	61.3±7.7	64.7±11.0
Pain on injection (frequency, %)	41	60	20

(1981), Rolly, Versichelen and Zubair (1980) and Briggs, Dundee and Clarke (1981), and slightly faster than those reported by Rutter and colleagues (1980) and Rogers and others (1980). Time to the loss of eyelash reflex was influenced by the amount of premedication and was significantly less when the oral and i.m. premedication was given than when patients were unpremedicated. The loss of eyelash reflex may not be a good end-point with diprivan as a mask can be applied to the face and other anaesthetics introduced when the patient stops counting. Premedication with droperidol and a narcotic in addition to diazepam caused the sleep produced by diprivan 2 mg kg^{-1} to be of sufficient duration to last for the 3-min period of observation. Another advantage of this premedication was the reduced frequency of pain on injection. It appears that pain on injection can be reduced in both its frequency and severity by previous administration of a narcotic and by injecting to the forearm rather than the hand.

Production of apnoea appears to be a feature of diprivan, since it occurred in 87% of the patients and lasted for the same amount of time regardless of the premedication used. A few patients were still apnoeic when they showed evidence of wakening from the injection.

Diazepam, droperidol and piritramide produced a slower control heart rate than the other premedications. Diprivan itself caused no change in heart rate from control in our study, which differs from an increase in heart rate reported by Major and colleagues (1981).

Most other investigators have reported, after diprivan, a decrease in arterial pressure of short duration which returned rapidly toward control. We also noted small decreases in mean arterial pressure which we considered to be clinically insignificant and which were returning toward control by the end of the 3-min observation period.

Although hypersensitivity reactions have been observed after injections of other drugs dissolved in cremophor, we observed no local or systemic reactions following injection of diprivan.

We conclude from this study that diprivan 2 mg kg^{-1} administered i.v. over 20 s produces rapid loss of consciousness regardless of the premedication used. This confirms the dose and speed of injection are the most important factors in determining time of induction. Premedication with a narcotic and tranquillizer had the advantage of making the sleep produced by diprivan more profound and reduced the frequency of pain on injection which is the most disturbing side-effect reported with diprivan. We consider this amount of premedication to be safe because we found no increase in effects on circulation or respiration or other side-effects which were clinically significant.

REFERENCES

Adam, H. K., Glen, J. B., and Hoyle, P. A. (1980). Pharmacokinetics in laboratory animals of ICI 35 868, a new intravenous induction agent *Br. J. Anaesth.*, 52, 743

Briggs, L. P., Dundee, J. W., and Clarke, R. S. J. (1981). Some observations with di-isopropyl phenol (ICI 35 868). *Br. J. Anaesth.*, 53, 183P.

Kay, B., and Adam, H. (1981). A dose–response relationship, and cumulation studies of Diprivan (ICI 35 868). *Br. J Anaesth.*, 53, 118P.

—— Rolly, G. (1977a). ICI 35 868, a new intravenous induction agent. *Acta Anaesthesiol. Belg.*, 28, 303

—— —— (1977b). ICI 35 868—The effect of a change of formulation on the incidence of pain after intravenous injection *Acta Anaesthesiol. Belg.*, 28, 317.

—— Stephenson, D. K. (1980). ICI 35 868 (Diprivan): a new intravenous anaesthetic. A comparison with Althesin. *Anaesthesia*, 35, 1182.

Major, E., Verniquet, A. J W., Waddell, T. K , Savege, T. M., Hoffler, D. E., and Aveling, W (1981). A study of three doses of ICI 35 868 for induction and maintenance of anaesthesia. *Br. J. Anaesth.*, 53, 267

Rogers, K. M., Dewar, K. M. S., McCubbin, T. D., and Spence, A. A. (1980) Preliminary experience with ICI 35 868 as an intravenous induction agent. Comparison with Althesin. *Br. J. Anaesth* , 52, 807.

Rolly, G., Versichelen, L., and Zubair, N. A. (1980). Use of ICI 35 868 as an anaesthetic induction agent. *Acta Anaesthesiol. Belg.*, 31, 241.

Runyon, R. D., and Haber, A. (1977). *Fundamentals of Behavioral Statistics*, 3rd edn, p. 288 Reading, Mass.: Addison-Wesley Pub. Co

Rutter, D. V., Morgan, M., Lumley, J., and Owen, R. (1980). ICI 35 868 (Diprivan): a new intravenous induction agent. A comparison with methohexitone. *Anaesthesia*, 35, 1188.

LES EFFETS DE LA PREMEDICATION SUR UNE INDUCTION AU DIPRIVANE

RESUME

Les effets de trois sortes de prémédications ont été comparés chez 45 patients en bonne santé chez qui l'anesthésie était induite par le diprivane 2 mg kg^{-1} i.v. La prémédication au diazépam 10 mg per os, associé au dropéridol 2,5–5 mg, et au piritramide 7,5–15 mg i m , entraînait une diminution de la douleur lors de l'injection et une anesthésie plus profonde avec le diprivane que le diazépam 10 mg per os, ou l'absence de prémédication. Il n'a pas été noté de différences dans la vitesse d'induction en utilisant comme stigmate de la perte de conscience le fait que le patient arrête de compter. En utilisant la perte du réflexe palpébral pour définir la perte de conscience, la prémédication orale et i.m. permettrait une induction plus rapide ($P < 0,05$) après diprivane ($39,3 \pm 2,9$ s) que l'absence de prémédication ($53,7 \pm 2,9$ s), sans que la fréquence des effets secondaires soit plus grande. La posologie et la vitesse d'injection sont les deux facteurs les plus importants qui influencent la vitesse d'induction.

DIE AUSWIRKUNGEN DER PRÄMEDIKATION AUF DIE EINLEITUNG MIT DIPRIVAN

ZUSAMMENFASSUNG

Die Auswirkungen von drei Pramedikationsweisen wurden bei 45 gesunden Patienten, bei denen die Narkoseeinleitung mit Diprivan i.v. 2 mg kg^{-1} durchgeführt wurde, verglichen. Pramedikation mit Diazepam 10 mg oral und Droperidol 2,5–5,0 mg und Piritramid 7,5–15,0 mg i.m. bewirkte geringeren Schmerz bei der Injektion und einen tieferen Schlaf auf Diprivan als mit Diazepam 10 mg oral oder ohne eine Prämedikation. Keine Unterschiede in der Geschwindigkeit der Einleitung wurden gefunden, wenn das Aufhören des Zählens als Zeichen für den Eintritt der Bewußtlosigkeit genommen wurde. Bei Verwendung des fehlenden Lidreflexes als Zeichen für den Eintritt der Bewußtlosigkeit ergab sich nach oraler und i.m. Pramedikation eine schnellere Narkoseeinleitung nach Gabe von Diprivan (39,3 ± 2,9 s) als ohne Prämedikation (53,7 ± 3,0 s) ohne daß mehr Nebenwirkungen auftraten. Die Dosis und die Injektionsrate sind die zwei wichtigsten Faktoren, die Einfluß auf die Geschwindigkeit der Narkoseeinleitung nehmen.

EFECTOS DE LA PREMEDICACION SOBRE LA INDUCCION POR DIPRIVAN

SUMARIO

Se compararon los efectos de diversos regímenes de premedicación en 45 pacientes a los que se indujo anestesia mediante 2 mg kg^{-1} de diprivan administrados intravenosamente. La premedicación mediante 10 mg de diazepam administrados oralmente, así como mediante 2,5–5,0 mg de droperidol y 7,5–15,0 mg de piritramide administrados intramuscularmente, produjeron un menor dolor durante la inyección y un sueño más profundo como consecuencia del diprivan que la producida por la premedicación con 10 mg de diazepam administrados oralmente o por la ausencia total de premedicación. No se hayaron diferencias en las velocidades de inducción cuando el cese de la cuenta se utilizó como signo de inconsciencia. Cuando se hizo uso de la pérdida de reflejos en el párpado para definir la inconsciencia, la premedicación oral e intramuscular aportó una inducción más rapida $P < 0{,}05$) después del diprivan (39,3 ± 2,9 segundos) que lo obtenido sin premedicación alguna (53,7 ± 3,0 segundos) y una mayor frecuencia de efectos secundarios. La dosis y el régimen de la inyección son los dos factores más importantes que influencian la velocidad de la inducción.