Br. J. Anaesth. (1982), 54, 303

EFFECT OF PREANAESTHETIC MEDICATION ON ANAESTHESIA WITH ICI 35 868

L. P. BRIGGS, M. BAHAR, H. T. B. BEERS, R. S. J. CLARKE, J. W. DUNDEE, P. J. WRIGHT, D. M. MCAULEY AND M. P. O'NEILL

SUMMARY

The effect of three commonly used premedicants and a control on anaesthesia with ICI 35 868 is described. Two randomized studies were performed—one a group study of induction characteristics at 2 mg kg^{-1} and the other a detailed study in patients undergoing minor gynaecological surgery with an induction dose of 1.5 mg kg^{-1} and maintenance with incremental doses plus 66% nitrous oxide in oxygen. Premedication had little effect on the already good induction characteristics. Only heavy opiate premedication produced reliable induction at 1.5 mg kg^{-1}, but with an increase in side-effects. Diazepam appears to be the premedicant of choice, although the overall frequency of pain on injection has not been affected by premedication.

ICI 35 868 (di-isopropyl phenol) is an i.v. anaesthetic agent, the clinical use of which was first described by Kay and Rolly in 1977. Animal studies had shown that it was similar to methohexitone in potency and toxicity, with little evidence of cumulation from repeated doses. Like thiopentone, effective doses cause sleep in one arm–brain circulation time (Briggs et al., 1981). It has recently been compared with Althesin (Kay and Stephenson, 1980) and with methohexitone (Rutter et al., 1980). Several clinical reports suggest that it is a drug with many promising features (Rutter et al., 1980; Major et al., 1981) and well worthy of further study.

In the early studies, Kay and Rolly (1977) found 1.0 mg kg^{-1} to be a satisfactory induction dose in unpremedicated patients. This is at variance with our own experience with the drug. In a dose-finding study, Briggs and colleagues (1981) found the minimum "sleep" dose to be 1.75 mg kg^{-1}, injected over 20 s. We recommended 2.0 mg kg^{-1} as the most satisfactory dose for routine clinical use, although Major and colleagues (1981) have since reported one failed induction out of 10 when this dose was given over 30 s. There have been no detailed studies on the influence of premedication on its clinical action and potency.

This paper reports an evaluation of the induction characteristics following our recommended dose of 2.0 mg kg^{-1} in patients given one of three commonly used premedicants and also the effect of these premedicants on a lower dose (1.5 mg kg^{-1}). This last was a well controlled randomized study involving only two anaesthetists in which ICI 35 868 was used as the main agent for a standard operation (detailed study), while the first studies involved a number of administrators who limited their observations to the immediate peri-induction period (group study).

METHODS

The patients in both studies were all fit adults aged 18–65 yr. They had no history of atopy or allergy nor had they received a Cremophor-containing anaesthetic in the previous 6 months. Informed consent was obtained from all patients. The induction doses were injected over a period of 20 s; the site of injection was noted and patients were asked if the injection was painful.

Premedicants. The four premedicant groups were: diazepam 10 mg given orally; pethidine 50–75 mg with atropine 0.6 mg i.m.; papaveretum 10–20 mg with hyoscine 0.2–0.4 mg i.m.; nil.

Detailed study. The patients were all undergoing minor gynaecological operations and anaesthesia was induced and maintained with ICI 35 868, with 66% nitrous oxide in oxygen, the

L. P. BRIGGS, L.R.C.P S.I., F.F.A.R.C.S.I; M. BAHAR, M.D., H. T. B. BEERS, M.B., F.F.A.R.C.S.I.; R. S. J. CLARKE, M.D., PH.D., F.F.A.R.C.S.; J. W. DUNDEE, M.D., PH.D., F.F.A.R.C.S., M.R.C.P.; P. J. WRIGHT, M.B., F.F.A.R.C.S., D. M. MCAULEY, M.B., F.F.A.R.C.S.; M. P. O'NEILL, M.B., F.F.A.R.C.S.I.; Department of Anaesthetics, The Queen's University of Belfast, N. Ireland

0007–0912/82/030303–04 $01.00

initial dose being 1.5 mg kg^{-1} followed by incremental doses of 10 mg as required to control reactive movements. The presence of excitatory effects (involuntary movements, tremor or hypertonus), respiratory upset (cough or hiccup) or respiratory depression (apnoea lasting for longer than 15 s) was noted. Arterial pressure was measured by auscultation before induction and at 1-min intervals throughout anaesthesia. The observations made during anaesthesia were standardized as in reported studies from this department (Dundee and Moore, 1961; Clarke et al., 1972; Zacharias et al., 1979). Patients were all followed up for 6 h and any untoward sequelae noted.

The patients were allocated at random to one of the four premedicant groups and active premedicants were given 60–90 min before operation. There were 20 patients in each of the active premedicant groups and 40 who received no premedication.

Group study. In patients of both sexes, undergoing a variety of operations anaesthesia was induced with ICI 35 868 2.0 mg kg^{-1}. Observations were as described above and the recordings were limited to a period of 2 min following induction, after which anaesthesia was continued with a variety of techniques. A total of eight anaesthetists took part in the study in which allocation to the various premedicant groups was again at random.

RESULTS

Detailed study. The patients in the four groups were broadly comparable with respect to average age, weight and duration of anaesthesia.

Only papaveretum with hyoscine premedication made 1.5 mg kg^{-1} a reliable induction dose (table I). The average total dose of ICI 35 868 was less in those patients given diazepam ($t = 2.85$; $P<0.01$) and papaveretum with hyoscine ($t = 5.96$; $P<0.001$) premedication than in the control group.

On the debit side, papaveretum with hyoscine premedication was associated with a greater frequency of marked respiratory depression than control ($\chi^2 = 43.8$; $P<0.001$), although it did not affect the frequency of notable reductions in arterial systolic pressure. It was also associated with a smaller number of patients who had control of their protective reflexes 2 min after discontinuing the nitrous oxide, although the difference from the other series was not statistically significant.

Group study. This was carried out in four sets, each of 50 patients, which were broadly comparable with respect to average age and weight (table II). Even the 2.0 mg kg^{-1} dose was not adequate

TABLE I. *Details of patients given induction doses of 1.5 mg kg^{-1} ICI 35 868 (mean ± SEM) and details of anaesthetic and postanaesthetic sequelae*

	Premedication			
	Nil	Diazepam	Pethidine–atropine	Papaveretum–hyoscine
No.	40	20	20	20
Age (yr)	35 ± 1.9	40 ± 2.2	34 ± 2.4	35 ± 2.4
Weight (kg)	60 ± 1.9	64 ± 2.2	62 ± 3 8	60 ± 1.6
Duration of anaesthesia (min)	9 5 ± 0.5	7.8 ± 0 5	9.6 ± 1 3	9 6 ± 0.7
Total dose (mg kg^{-1})	3.0 ± 0 12	2.5 ± 0.13	3.2 ± 0.24	2.0 ± 0 09
Anaesthesia induced	35	19	17	20
Marked respiratory depression	2	3	0	6
Decrease in systolic AP > 20 mm Hg	5	4	2	3
After operation				
"Safe" 2 min after nitrous oxide off	34	19	17	15
Nausea or vomiting, or both (0–6 h)	3	0	1	2

TABLE II. *Details of patients given induction doses of ICI 35868 2 mg kg^{-1} in group study (mean ± SEM) and details of anaesthetic sequelae. There were 50 patients in each series*

	Premedication			
	Nil	Diazepam	Pethidine–atropine	Papaveretum–hyoscine
Age (yr)	37 ± 1 9	37 ± 2 3	39 ± 2.1	38 ± 2.2
Weight (kg)	60 ± 1.6	60 ± 1.5	61 ± 1 3	61 ± 1 6
Anaesthesia induced	45	50	49	49
Marked respiratory depression	1	0	13	11
Decrease in systolic pressure > 20 mm Hg	10	11	12	23

TABLE III *Frequency of pain on injection related to injection site (pooled data from both studies)*

	Premedication			
Site of injection	Nil	Diazepam	Pethidine–atropine	Papaveretum–hyoscine
Antecubital fossa				
Total number	21	22	33	26
Pain	3	0	2	2
Hand or wrist				
Total number	20	11	17	26
Pain	6	3	7	11

to ensure a consistent induction of anaesthesia in unpremedicated patients. Any form of opiate premedication increased the frequency of marked respiratory depression to a significant extent ($P < 0.01$), while premedication with papaveretum and hyoscine was associated with more frequent hypotension than in the other two groups ($P < 0.001$).

The overall frequency of reductions in arterial systolic pressure in excess of 20 mm Hg was 28% in patients induced with 2 mg kg^{-1} compared with 14% of those given 1.5 mg kg^{-1}, but this difference was not statistically significant.

The pooled data from the two studies relating the frequency of injection site pain to the site of injection (table III) shows a highly significant difference ($P < 0.001$) between the frequency with antecubital fossae injections (9%) and those given in the hand or wrist (31%).

DISCUSSION

Compared with drugs such as methohexitone, minaxolone and etomidate, ICI 35868 can be classed as a good induction agent with minimal involuntary movement following normal doses. There is thus little room for improvement with premedication, nor is it an essential part of the anaesthetic technique. In fact papaveretum with hyoscine premedication introduces undesirable side-effects, although it does make the smaller dose (1.5 mg kg^{-1}) acceptable for induction. Of those agents studied diazepam would appear to be the premedication of choice with ICI 35868.

It is unfortunate that analgesic premedication does not influence the pain experienced when ICI 35868 is injected into small veins of the hand and wrist. The overall frequency of pain in this study was identical with that reported by Briggs and others (1981) and, when the two series were combined, giving the frequency of pain as 5% with antecubital injections and 37% with hand or wrist injections, the need for an alternative pain-free formulation became more obvious.

ACKNOWLEDGEMENTS

We are grateful to Imperial Chemical Industries, Pharmaceuticals Division for their co-operation and supplies of the drug, in particular Drs Malcolm Peet and Ron Stark We would also like to thank the medical and nursing staff of all the Belfast Teaching Hospitals for their understanding and assistance.

REFERENCES

Briggs, L P., Clarke, R. S J , Dundee, J. W., Moore, J., Bahar, M., and Wright, P J (1981) Use of di-isopropyl phenol as main agent for short procedures *Br. J. Anaesth.*, **53**, 1197

Clarke, R S J., Dundee, J. W., Carson, I. W , Arora, M. V , and McCaughey, W (1972) Clinical studies of induction agents XL· Althesin with various premedicants *Br. J Anaesth* , **44**, 845.

Dundee, J. W., and Moore, J. (1961). Thiopental and methohexital a comparison as main agents for a standard operation *Anaesthesia,* **16**, 50.

Kay, B., and Rolly, G (1977). ICI 35868, a new intravenous induction agent *Acta Anaesthesiol. Belg.*, **28**, 303

—— Stephenson, D. K (1980) ICI 35868 (Diprivan). a new intravenous agent. 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 35868 for induction and maintenance of anaesthesia. *Br J Anaesth.*, **53**, 267

Rutter, D. V., Morgan, M., Lumley, J., and Owen, R. (1980) ICI 35868 (Diprivan) a new intravenous agent. A comparison with methohexitone *Anaesthesia,* **35**, 1188

Zacharias, M , Dundee, J W., Clarke, R S J., and Hegarty, J E. (1979) Effect of preanaesthetic medication on etomidate *Br J. Anaesth* , **51**, 127.

EFFETS DE LA PREMEDICATION SUR L'ANESTHESIE AU ICI 35868

RESUME

On décrit les effets de trois agents couramment utilisés en prémedication et d'un témoin sur l'anesthésie à l'ICI 35868. Deux etudes randomisées ont été faites, une étude de groupe des caracteristiques d'induction a $2\,mg\,kg^{-1}$, et une étude détaillée chez des sujets subissant des actes de chirurgie gynecologique mineure avec une dose d'induction de $1{,}5\,mg\,kg^{-1}$ et un entretien par des doses croissantes associées à 66% de protoxyde d'azote dans l'oxygène. La prémédication a peu d'effet sur les caracteristiques d'induction déjà bonnes. Seule une prémédication morphinomimétique lourde permet une induction fiable à $1{,}5\,mg\,kg^{-1}$ mais au prix d'une augmentation des effets secondaires. Le diazepam apparait comme l'agent de prémédication de choix bien que la fréquence globale de douleur à l'injection n'ait pas été modifiée par la prémedication

DIE WIRKUNG EINER PRAMEDIKATION AUF DIE ANÄSTHESIE MIT ICI 35868

ZUSAMMENFASSUNG

Die Wirkung von drei allgemein gebräuchlichen Medikamenten in Zusammenhang mit einer ICI 35868 Anästhesie wird beschrieben Zwei randomisierte Untersuchungen wurden durchgeführt. In der einen Gruppe wurde die Einleitung mit $2\,mg\,kg^{-1}$, in der anderen eine detaillierte Studie an Patienten, die sich einer kleinen gynäkologischen Operation unterzogen hatten, durchgeführt. Bei diesen wurde die Einleitungsdosierung auf $1{,}5\,mg\,kg^{-1}$ festgesetzt und die Aufrechterhaltung mit zunehmender Dosierung in Kombination von 66% Stickoxydul in Sauerstoff erreicht. Die Prämedikation hatte geringe Wirkung auf die bereits guten Einleitungseigenschaften Nur eine starke Prämedikation mit Opiaten zeigte eine verlässliche Induktion bei $1{,}5\,mg\,kg^{-1}$, jedoch nahmen die Nebenwirkungen zu Diazepam scheint die Prämedikation der Wahl zu sein, obwohl die allgemeine Inzidenz des Injektionsschmerzes durch die Prämedikation nicht beeinflusst werden konnte.

EFECTO DE LA MEDICACION PREANESTETICA SOBRE LA ANESTESIA CON ICI 35868

SUMARIO

Se describe el efecto de tres substancias de premedicación común y el control de la anestesia con ICI 35868. Se llevaron a cabo dos estudios al azar—uno en un estudio de grupo de caracteristicas de inducción con $2\,mg\,kg^{-1}$, y el otro un estudio detallado en pacientes sometidos a operaciones ginecológicas menores con una dosis de inducción de $1{,}5\,mg\,kg^{-1}$, y mantenimiento con dosis incrementadas además de un 66% óxido nitroso en oxigeno. La premedicación tuvo poco efecto sobre las caracteristicas yá buenas de la inducción. Una premedicación fuerte con opiatos sólo produjo una inducción fiable con $1{,}5\,mg\,kg^{-1}$, pero con un aumento de los efectos secundarios. El diazepam parece ser la substancia de premedicación la más selecta, aunque la frecuencia general del dolor al momento de la inyección no fue afectada por la premedicación.