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USE OF DI-ISOPROPYL PHENOL AS MAIN AGENT FOR SHORT PROCEDURES

L. P. BRIGGS, R. S. J. CLARKE, J. W. DUNDEE, J. MOORE, M. BAHAR AND P. J. WRIGHT

SUMMARY

The use of di-isopropyl phenol (Diprivan) for induction of anaesthesia was assessed in doses ranging from 1 to 3 mg kg^{-1}. With less than 1.75 mg kg^{-1} not all patients were anaesthetized; 2.0 mg kg^{-1} appeared to be a satisfactory induction dose. Involuntary muscle movement, cough and hiccup at induction were rare with any dose studied. However, the frequency of hypotension and respiratory depression were related to the dose given. Pain on injection was uncommon when the drug was given into an antecubital vein, but occurred in 39% of patients when injected to the back of the hand or wrist. Recovery was rapid, and characterized by lack of emetic sequelae. Di-isopropyl phenol 1.5–2.0 mg kg^{-1} given rapidly during reactive hyperaemia can produce anaesthesia in one arm–brain circulation time. A reaction involving flush, hypotension, cough, laryngospasm and bronchospasm occurred in one patient receiving 2.5 mg kg^{-1} given over 20 s.

Di-isopropyl phenol (Diprivan; ICI 35 868) is an i.v. anaesthetic, sparingly soluble in water. Its clinical use was first described in 1977 by Kay and Rolly. Animal studies had shown that it was similar to methohexitone in potency and toxicity, with little evidence of cumulation. Kay and Rolly (1977a) found the optimum dose to be 1 mg kg^{-1}, which produced few side-effects and rapid recovery. However, with the original 2% formulation, in Cremophor EL and ethanol, pain occurred frequently along the vein to which the drug had been injected (Kay and Rolly, 1977b). This was found to be partly caused by the solvent and when a more dilute solution of 1% di-isopropyl phenol in Cremophor EL was used, the frequency and severity of pain on injection decreased to a level similar to that for methohexitone. Its animal pharmacology was described by Glen (1980) and preliminary findings in man by Rogers and his colleagues (1980). It has recently been compared with Althesin (Kay and Stephenson, 1980) and with methohexitone (Rutter et al., 1980).

The present study was designed to assess the optimum induction dose of di-isopropyl phenol and its local and general side-effects over a range of doses. In addition, speed and quality of recovery were assessed.

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Rapidity of onset is desirable in an i.v. anaesthetic since it allows the dose to be titrated against effect during induction. A separate investigation was undertaken to determine the rate of onset of anaesthesia with di-isopropyl phenol.

METHODS

Healthy women undergoing minor gynaecological operations gave informed consent for the administration di-isopropyl phenol; any patient with a history of atopy or allergy (Watkins, Clarke and Fee, 1981) was excluded. As a result of previous reports of reactions with Cremophor-containing solutions (Huttel, Schou Oleson and Stoffersen, 1980) and the study by Glen and his colleagues (1979) on hypersensitivity reactions in the "mini-pig", any patient who had received a Cremophor-containing anaesthetic in the previous 6 months was also excluded.

Patients were not premedicated and were allocated at random to receive one of the selected doses (table I). The duration of anaesthesia and average total dose of the maintenance anaesthetic were broadly comparable. Di-isopropyl phenol was injected over 20 s to a convenient vein in the arm or hand. Each patient was asked "Is your arm quite comfortable?" and any complaint of pain was noted.

Anaesthesia was maintained with nitrous oxide 67% in oxygen and further 1-ml doses of the induction agent as required. If the patient failed to lose consciousness within 60 s, this was regarded as

TABLE I. *Details of patients given a range of anaesthetic doses of di-isopropyl phenol*

Dose	1.0	1.5	1.75	2.0	2.5	3.0
Number	20	20	20	40	20	20
Average age (yr)	37	32	29	33	34	36
Average weight (kg)	58	59	59	58	60	60
Average total dose ($mg\,kg^{-1}$)	3.1	3.2	3.3	3.5	3.3	3.4
Average duration (min)	9.0	9.1	8.0	9.9	8.5	6.4

absence of anaesthesia. The presence of excitatory effects (involuntary movements, tremor or hypertonus), respiratory upset (cough or hiccup) or respiratory depression (apnoea lasting for more than 15 s) was noted. Arterial pressure was measured by auscultation before induction and at 1-min intervals throughout anaesthesia.

At the end of surgery, the administration of nitrous oxide was discontinued and 2 min later each patient was assessed as awake, unconscious but with jaw tone, or unconscious without protective reflexes. At 1-min intervals the patient was asked to open her eyes and to give her date of birth, and the time was noted when she responded to these commands. The patient was questioned about nausea and vomiting approximately 1 and 6 h after the end of surgery.

The rate of onset of anaesthesia was investigated by injecting the drug to a large forearm vein as rapidly as possible during reactive hyperaemia following 3 min of circulatory occlusion (Clarke et al., 1968). In this way, the drug was carried rapidly centrally and the arm–brain circulation time was shortened and standardized. The onset time was studied in three groups of 20 patients with doses of 1.5, 1.75 and 2.0 $mg\,kg^{-1}$ injected rapidly (1–3 s). The time from end of injection to cessation of counting was noted and, if the patient was not anaesthetized, the time was counted for averaging as 20 s.

RESULTS

Anaesthesia was successfully induced with the larger doses of ICI 35868, but with the 1.0- and 1.5-$mg\,kg^{-1}$ doses some patients failed to go to sleep (table II) and remained with the eyes open or talked or moved purposefully. There were few involuntary muscle movements, hiccup or other excitatory effects in any group and their occurrence was not dose-related. However, respiratory depression was dose-related and was

TABLE II. *Percentage of patients with various induction characteristics after a range of doses of di-isopropyl phenol given over 20 s*

	Dose ($mg\,kg^{-1}$)					
	1.0	1.5	1.75	2.0	2.5	3.0
Anaesthesia induced	25	80	100	100	100	100
Excitatory effect	0	0	0	0	5	0
Respiratory upset	0	0	5	5	5	0
Marked respiratory depression	0	5	0	13	15	75
Decrease in systolic art. press. (mm Hg)						
20–40	0	5	0	5	30	50
40+	0	0	0	0	5	15

marked in 75% of patients receiving 3.0 $mg\,kg^{-1}$. The maximum duration of apnoea was 2 min with 3.0 $mg\,kg^{-1}$ and ventilation of the lungs was assisted easily in all patients. Hypotension was rare with doses up to 2 $mg\,kg^{-1}$, but was more frequent and severe as the dose was increased. The maximum decrease in systolic pressure was 50 mm Hg.

The frequency of pain on injection is shown in table III. Most of the patients complained of pain after 10–20 s and it extended along the vein of injection. The frequency of pain was 39% following injection to the back of hand or wrist and 3% following injection to one of the antecubital veins

TABLE III. *Number of patients who complained of pain on injection after di-isopropyl phenol given to veins of various size at various sites (pooled doses)*

Site	Size	Patients	Number complaining of pain on injection
Antecubital	Large	73	3
	Medium	43	1
	Small	1	0
Wrist/hand	Medium	21	7
	Small	2	2
Total		140	13

($\chi^2 = 29.1$; $P < 0.0005$). There was no clear relation between size of vein and pain.

With the doses of di-isopropyl phenol used in this study, recovery was rapid (table IV), nearly all the patients having regained the protective reflexes 2 min after discontinuing nitrous oxide. Ability to

TABLE IV. *Recovery after a range of doses of di-isopropyl phenol*

	Dose ($mg\,kg^{-1}$)					
	1.0	1.5	1.75	2.0	2.5	3.0
2 min after anaesthesia:						
Awake (%)	50	40	15	25	35	30
Safe (%)	50	50	70	70	65	70
Time (min) to:						
Opening eyes on command	2.8	2.9	4.0	4.2	3.1	4.2
Giving date of birth	4.6	4.3	5.4	5.5	4.4	5.9
During first 6 h:						
Nausea (%)	0	10	10	5	0	0
Vomiting (%)	20	5	5	0	5	0

answer questions on the date of birth returned rapidly. The total dose of di-isopropyl phenol was similar in each group and recovery time was not related to the initial dose (table IV). Postoperative nausea and vomiting were rare but were more apparent with smaller doses.

When di-isopropyl phenol was given as rapidly as possible in adequate doses ($1.75–2.0\,mg\,kg^{-1}$), it produced anaesthesia in one arm–brain circulation time (table V). The smaller dose ($1.5\,mg\,kg^{-1}$) failed to induce anaesthesia in one patient and the average time for onset of anaesthesia was longer.

TABLE V. *Time (mean ± SEM) to cessation of counting in three groups of 20 patients given di-isopropyl phenol as rapidly as possible during reactive hyperaemia*

	Dose ($mg\,kg^{-1}$)		
	1.5	1.75	2.0
Average age (yr)	38	33	40
Average weight (kg)	64	59	60
Onset of anaesth. (s)	13.5 ± 0.70	11.9 ± 0.58	10.5 ± 0.38

One of the patients who received di-isopropyl phenol $2.5\,mg\,kg^{-1}$ over 20 s had an anaphylactoid reaction involving coughing which began 1 min following induction. Two minutes later the patient was given a further 20 mg on the assumption that anaesthesia was light, but further coughing with laryngospasm and bronchospasm followed. Cyanosis developed and persisted in spite of giving oxygen only to breathe. Three minutes after induction an urticarial rash was seen over the whole body. Arterial systolic pressure decreased from 110 mm Hg to 60 mm Hg at 3 min after the initial injection and hydrocortisone 500 mg, chlorpheniramine 10 mg and a rapid infusion of isotonic sodium lactate were given i.v.

The operative procedure was continued without nitrous oxide or further i.v. anaesthesia and recovery was uneventful, with opening of eyes 14 min after induction. Bronchospasm had disappeared completely within 20 min of anaesthesia; by this time some swelling of the eyelids which persisted for 12 h had developed. One week later the patient was anaesthetized for hysterectomy with thiopentone, pancuronium, fentanyl and nitrous oxide in oxygen. The anaesthetic was uneventful.

This patient, like all the others given di-isopropyl phenol in this study, had no history of atopy or allergy and no previous exposure to a Cremophor-containing anaesthetic. She appeared to be healthy. Plasma samples were taken serially and analysed for immunoglobulins and complement components (Watkins, Thornton and Clarke, 1979). The results, which suggest a true hypersensitivity, will be described elsewhere.

DISCUSSION

First studies with a new i.v. anaesthetic must be concerned with its potency and with determining a suitable anaesthetic dose. It was soon apparent that doses of less than $1.75\,mg\,kg^{-1}$ of di-isopropyl phenol did not produce anaesthesia consistently. This is in contrast to the finding of Kay and Rolly (1977a) that $1.0\,mg\,kg^{-1}$ was satisfactory. There is no obvious reason for this discrepancy other than a different criterion for minimum sleep dose. Certainly, for clinical practice, $2.0\,mg\,kg^{-1}$ would be the most satisfactory induction dose and would appear to be comparable to thiopentone $4–5\,mg\,kg^{-1}$.

Di-isopropyl phenol can be classed as a rapidly-acting drug with an onset time comparable to that of thiopentone or methohexitone (Clarke et al., 1968) and quite different from ketamine (Bovill et al., 1971). This adds to the safety of the drug and its acceptability in clinical practice. Apart from drugs with slow onset of action such as ketamine or diazepam, onset of anaesthesia in clinical practice depends more on haemodynamic than on drug factors, as can be seen from the rapid injection studies.

Unlike some other induction agents evaluated in the past 20 years, such as methohexitone, etomidate or Althesin, di-isopropyl phenol does not evoke excitatory effects or hiccup in any of the doses studied. There were fewer side-effects than with thiopentone which has for long been regarded as ideal in this respect. However, there is a dose-related respiratory depression which is of no clinical importance at normal induction doses but becomes marked at 3.0 mg kg^{-1}. At this dose, 75% of patients exhibited apnoea lasting for more than 15 s and required ventilatory assistance. This is certainly more marked than with comparable doses of thiopentone, for only with thiopentone 14 mg kg^{-1} preceded by an opiate was such a degree of respiratory depression found (Clarke and Dundee, 1970). Further studies are needed to investigate this effect of di-isopropyl phenol. Arterial hypotension is not clinically important with a dose of 2.0 mg kg^{-1} but is marked with a dose of 3.0 mg kg^{-1}.

Pain on injection was a prominent feature of early reports of ICI 35868 (Kay and Rolly, 1977a, b). This was probably caused partly by the use of the 2% formulation of Cremophor EL with ethanol, but the adoption of the 1% formulation in Cremophor alone reduced injection pain to a level comparable to methohexitone (Kay and Rolly, 1977b). The present study has shown that pain on injection is still a marked disadvantage of the drug when given to peripheral arm veins. This relationship to site of injection rather than vein size may reflect that the pain does not develop for about 20 s and with more proximal injections the patient is usually asleep by this time. Certainly it was absent with the very rapid injection through a large cannula, and further (unpublished) observations suggest that it is more frequent with injections over 30–40 s. Alternatively it could be related to the rate of dilution which would be more rapid following injection to an antecubital than to a hand vein. The use of etomidate is also accompanied by pain and injections to the hand led to more pain than those into the forearm. Pain was also more frequent with small veins and slow injection speeds (Zacharias et al., 1978, 1979). There was no relationship in individual patients between pain on injection following etomidate and the development of phlebitis (Zacharias et al., 1979). It is therefore not surprising that studies of venous sequelae with di-isopropyl phenol have shown no relationship to previous pain and we found venous sequelae to be very rare.

Recovery following di-isopropyl phenol is satisfactory, although in our study few patients were awake 2 min after discontinuing nitrous oxide. The actual percentage varied between 25 and 50% whereas Dundee (1963), comparing all the barbiturates found a range between 30% for hexobarbitone and 80% for methohexitone. However, the majority of patients had regained protective reflexes at 2 min. There are no comparable figures yet for recovery of mental clarity, but the ability to give date of birth returned between 4 and 6 min after the end of anaesthesia which is very satisfactory clinically. The almost total absence of emetic sequelae (and often a desire for food) after anaesthesia with this drug is a major feature in its acceptability to the patient.

Di-isopropyl phenol is a drug with some advantages over existing induction agents, in particular the absence of excitatory effects and rapid recovery, free from sickness. However, the frequency of pain on injection is undesirable and the cardiovascular and respiratory despression when the normal induction dose is exceeded suggest a smaller safety margin than with Althesin.

The most important objection to di-isopropyl phenol is the use of Cremophor EL in the formulation. Evidence is accumulating to associate this solvent with hypersensitivity reactions (Watkins et al., 1976; Glen et al., 1979) and it is therefore highly desirable to find another solubilizing agent. The reaction encountered was not dangerous to the patient and resembles closely those seen with Althesin, but further reactions are to be anticipated. Since di-isopropyl phenol rather than the Cremophor EL is likely to cause pain on injection, this pain may remain as an undesirable feature, but it is brief in duration, whereas the hypersensitivity reactions are potentially life-threatening.

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REFERENCES

Bovill, J. G., Coppel, D. L., Dundee, J. W., and Moore, J. (1971). Current status of ketamine anaesthesia. *Lancet*, 1, 1285.

Clarke, R. S. J., and Dundee, J. W. (1970). Toxic effects of intravenous anaesthetics: a comparison of propanidid with thiopentone; *Progress in Anaesthesiology: Proceedings of the Fourth World Congress of Anaesthesiologists* London, September 1968, p. 1189. Amsterdam: Excerpta Medica.

—— —— Barron, D. W., and McArdle, L (1968). Clinical studies of induction agents. XXVI: The relative potencies of thiopentone, methohexitone and propanidid. *Br. J. Anaesth.*, **40**, 593.

Dundee, J. W. (1963). Clinical studies of induction agents, VII: A comparison of eight intravenous anaesthetics as main agents for a standard operation. *Br. J. Anaesth.*, **35**, 784.

Glen, J. B. (1980). The animal pharmacology of ICI 35868: a new i.v. anaesthetic agent. *Br. J. Anaesth.*, **52**, 230P.

—— Davies, G. E., Thomson, D. S., Scarth, S. C., and Thompson, A. V. (1979). An animal model for the investigation of adverse responses to i.v. anaesthetic agents and their solvents. *Br. J. Anaesth.*, **51**, 819.

Huttel, M. S., Schou Oleson, A. S., and Stoffersen, E. (1980). Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid M. R.). *Br. J. Anaesth.*, **52**, 77.

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

—— —— (1977b). ICI 35868—the effect of a change of formulation on pain after intravenous injection. *Acta Anaesthesiol. Belg.*, **28**, 317.

—— Stephenson, D. K. (1980). ICI 35868 (Diprivan): a new intravenous agent. A comparison with Althesin. *Anaesthesia*, **35**, 1182.

Rogers, K. M., Adam, H. K., Dewar, K. M. S., Kay, B., McCubbin, T. D., Spence, A. A., and Stephenson, D. (1980). ICI 35868, a new i.v. anaesthetic: preliminary findings in 20 patients. *Br. J. Anaesth.*, **52**, 230P.

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.

Watkins, J., Clark, A., Appleyard, T. N., and Padfield, A. (1976). Immune-mediated reactions to Althesin (Alphaxalone). *Br. J. Anaesth.*, **48**, 881.

—— Clarke, R. S. J., and Fee, J. P. H. (1981). The relationship between reported atopy or allergy and immunoglobulins: a preliminary study. *Anaesthesia*, **35**, 582.

—— Thornton, J. A., and Clarke, R. S. J. (1979). Adverse reactions to i.v. agents. *Br. J. Anaesth.*, **51**, 469.

Zacharias, M., Clarke, R. S. J., Dundee, J. W., and Johnston, S. B. (1978). An evaluation of three preparations of etomidate. *Br. J. Anaesth.*, **50**, 925.

—— —— —— —— (1979). Venous sequelae following etomidate. *Br. J. Anaesth.*, **51**, 779.

USAGE DU DI-ISOPROPYLE PHENOL COMME AGENT ANESTHESIANT PRINCIPAL POUR LES INTERVENTIONS CHIRURGICALES DE COURTE DUREE

RESUME

On a fait usage de di-isopropyle phénol (Diprivan) pour l'induction de l'anesthésie en doses allant de 1 à 3 mg kg^{-1}. Avec moins de 1,75 mg kg^{-1}, il n'a pas été possible d'anesthésier tous les patients, mais 2 mg kg^{-1} semble avoir été une dose d'induction satisfaisante. Les mouvements musculaires involontaires, la toux et le hoquet, au moment de l'induction, ont été rares, quelle que soit la dose étudiée. Toutefois, la fréquence de l'hypotension et celle de la dépression respiratoire ont pu être reliées à la dose administrée. La douleur au moment de l'injection n'a pas été courante, lorsque cette injection a été faite dans une veine antécubitale, mais elle a été constatée dans 39% des cas, lorsque l'injection a été faite dans le dos de la main ou dans le poignet. La récupération a été rapide et a été caractérisée par un manque de séquelles émétiques. Le di-isopropyle phénol à raison de 1,5–2 mg kg^{-1} administré rapidement pendant une hyperémie réactive peut produire l'anesthésie dans un temps de circulation bras–cerveau. Il s'est produit une réaction entraînant bouffées de chaleur, hypotension, toux, laryngospasme et bronchospasme chez un malade auquel on avait administré 2,5 mg kg^{-1} en 20 secondes.

DIE VERWENDUNG VON DI-ISOPROPYLPHENOL ALS HAUPTNARKOSEMITTEL BEI KURZEN OPERATIONEN

ZUSAMMENFASSUNG

Di-Isopropylphenol (Diprivan) wurde in Dosen zwischen 1–3 mg kg^{-1} zur Induktion der Anästhesie verwendet. Bei weniger als 1,75 mg kg^{-1} wurden nicht alle Patienten betäubt; 2,0 mg kg^{-1} scheint eine hinreichende Induktionsdosis darzustellen. Unwillkürliche Muskelbewegungen, Husten und Schluckauf bei der Induktion kamen selten vor bei den Dosen, die hier studiert wurden. Die Häufigkeit von Hypertropie und Atmungsdepression stand jedoch in Beziehung mit den verabreichten Dosen. Als die Droge in eine vorulnäre Vene injiziert wurde, gab es selten Schmerzen, aber 39% der Patienten empfanden Schmerzen, als die Droge in den Handrücken oder in das Handegelenk injiziert wurde. Sie erholten sich aber schnell und ohne Brechreiz. Wenn Di-Isopropylphenol 1,5–2,0 mg kg^{-1} schnell während reaktiver Hyperämie verabreicht wird, kann die Anästhesie mit Zirkulationsgeschwindigkeit eintreten. Eine Reaktion, die aus Röte, Hypertropie, Husten, Laryngospasmus und Brochospasmus bestand, stellte sich bei einem Patienten ein, der 2,5 mg kg^{-1} innerhalb 20 Sekunden bekam.

USO DEL DI-ISOPROPILA FENOLICO CUAL AGENTE PRINCIPAL PARA PROCEDIMIENTOS DE CORTA DURACION

SUMARIO

El uso de di-isopropilo fenólico (Diprivan) para inducir anestesia se administró en dosis que oscilaron entre 1 y 3 mg kg^{-1}. No todos los pacientes quedaron anestesiados cuando se les administro una cantidad inferior a 1,75 mg kg^{-1}; la dosis de inducción que pareció ser satisfactoria fue de 2,0 mg kg^{-1}.Con todas las dosis que se estudiaron, el movimiento muscular involuntario, la tos y el hipo, durante la inducción, fueron algo poco frecuente. No obstante, la frecuencia de la hipotensión y de la depresión respiratoria vinieron relacionadas con la dosis administrada. El dolor como consecuencia de la inyección fue poco común cuando la droga se administró en una vena antecubital, pero se presentó en el 39% de los pacientes cuando la inyección se efectuó en la parte

posterior de la mano o de la muñeca. La recuperación fue rápida y se caracterizó por la falta de secuelas eméticas. El diisopropilo fenólico, en dosis de 1,5–2,0 mg kg^{-1}, administrados rápidamente durante la hiperemia reactiva, puede producir anestesia en el tiempo correspondiente a la circulación entre el brazo y el cerebro. Se presentó una reacción en la que aparecieron enrojecimiento de las mejillas, hipotensión, tos, espasmos de la laringe y espasomos de los bronquios en un paciente al que se le administraron 2,5 mg kg^{-1} durante un período de 20 segundos.