

Clinical Evaluation of Isoflurane DEMOGRAPHY OF PATIENT POPULATION

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SINCE THE AIM of the clinical evaluation of isoflurane was to assess its efficacy and safety in a wide spectrum of clinical situations, the participants in this study were asked to administer the drug to an unselected group of patients. Thus, for each institution, the patients were intended to be representative of the normal surgical and anaesthesia population, including elective and emergency cases, all ages and all procedures. The only restriction was that obstetrical patients were not to be included. It was anticipated and confirmed by the interim analyses on sequential cohorts that the initial use of isoflurane would be mainly confined to low risk elective procedures. As experience was gained in the clinical use of isoflurane, the original aims of the study were achieved by inclusion of all types of procedures, all ASA categories and all ages.

In addition to the overall analysis of global data, for all participating institutions, the data from each institution were analysed separately to examine the impact of interinstitutional variation. The data from geographic regions (Canada, North East, North Central, Southern and Western regions of the United States) were analysed separately to determine variations in patient factors, such as incidence of diseases, current medications and age, as well as variations in anaesthetic factors such as the anaesthetic drugs used, concentrations of isoflurane used, and duration of anaesthesia. The results of this geographic analysis are reported in a separate section in this report since they have provided new information of epidemiological significance.

DEMOGRAPHIC SUMMARY

There were 7,196 cases where isoflurane was administered in this study, which was carried out in 165 university teaching hospitals throughout the United States and Canada. A total of 6,798 cases were fully analysed and are reported here. The remaining 398 cases had unresolved errors on the evaluation form but were examined with

the global analysis programme, including documentation of complications.

The patients in the study ranged in age from the neonate to over 100 years (mean \pm 1SD = 39.5 ± 21.5), in weight from less than 1 kg to 218 kg (mean \pm 1SD = 63.8 ± 23.1), in height from 24 cm to 203 cm (mean \pm 1SD = 160 ± 24.8), and in body surface area from 0.08 m^2 to 3.12 m^2 (mean \pm 1SD = 1.66 ± 0.41). The proportion of males to females overall was 45.9 per cent and 54.1 per cent respectively, although this varied with age. The physical status of patients was predominantly in ASA categories 1 and 2 (81.2 per cent) with a relatively small proportion of the total being emergencies (4.7 per cent). Table 1 lists the number of patients by age group and ASA status with the proportion of males indicated (see also Figure 1).

DISEASE AREAS RECORDED

Most patients (75.8 per cent) had some coexisting disease recorded. The remaining 24.2 per cent had no disease listed. The most frequent system with disease was circulatory (22.3 per cent) with other systems having frequencies of less than half of this. Table 2 lists the proportions of patients with recorded disease.

CURRENT MEDICATION

A total of 1,645 patients had no disease and no current medication. There were a further 1,591 patients (23.4 per cent) who smoked. Thus the total number of patients not taking any of the listed cardiac or respiratory drugs was 3,691 (54.3 per cent). Approximately 1 in 10 patients (9.8 per cent) were on diuretics at the time of study while 1 in 20 (5.2 per cent) were on beta blocking drugs. Table 2 lists the proportion of patients on these listed drugs.

ANAESTHETIC DRUGS

Table 3 summarizes the drugs used for premedication, induction of anaesthesia and main-

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TABLE 1

Age (yr)	<1	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100+
#	135	639	558	1218	1081	874	1009	746	413	108	16
%M	75	60.2	50.0	37.8	36.5	39.5	51.0	52.7	49.2	45.4	35.7
ASA Status	1		2		3		4		5		ALL
Non E	3060		2263		1040		112		1		6476
E	108		90		95		29		0		322
Total	3168		2353		1135		141		1		6798
%	46.6		34.6		16.7		2.1		0		

Mean age (± 1 SEM) yr = 39.48 ± 0.26 (Range 0-104)
 Mean wt (± 1 SEM) kg = 63.78 ± 0.28 (Range <1-218)
 Mean ht (± 1 SEM) cm = 160.00 ± 0.31 (Range <24-217)
 Mean surface (± 1 SEM) m² = 1.66 ± 0.005 (Range 0.08-3.12)

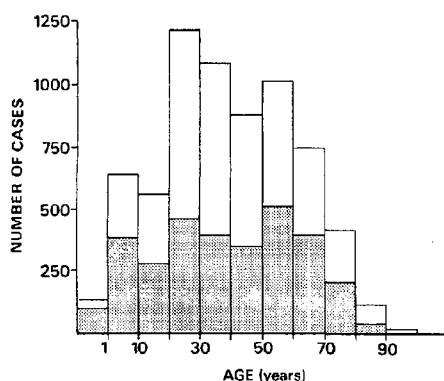


FIGURE 1 Distribution of total number of cases by decade and for those under 1 year old, with the number of males shown by the shaded areas.

tenance. A total of 1,380 (20.3 per cent) of patients did not have premedication while 1,149 (16.9 per cent) had no drugs administered at induction other than isoflurane with oxygen and nitrous oxide. The most frequent premedicant drug was narcotic (57 per cent of cases) followed by tranquilizer (46.8 per cent) and anticholinergics (45.9 per cent). The percent values given in Table 3 are for all possible combinations of drugs. Alfathesin was used infrequently for induction (0.5 per cent) while the most common induction agent by far was barbiturate (76.5 per cent). Anticholinergics were fairly commonly given during maintenance (21.1 per cent) as were relaxant antagonists (19.9 per cent).

The proportion of patients who had tracheal intubation was high in each period of anaesthesia (75.4 per cent at induction and 62.9 per cent during maintenance) with similar high proportions being ventilated (62.4 per cent at induction

TABLE 2
DISEASE AREAS
PERCENTAGE OF ALL CASES

Respiratory	11.8
Hepatic	3.3
Circulatory	22.3
Renal	5.8
CNS	6.5
Endocrine	6.0
GI	10.5
Gynecology	12.6
Ortho	11.9
Other	16.2
No Disease	24.2

CURRENT MEDICATION
PERCENTAGE OF ALL CASES

Digitalis	3.0
Beta block	5.2
Diuretic	9.8
Nitrate	3.1
Bronchodilator	1.7
Smoker	23.4
No drugs	54.3

TABLE 3
ANAESTHETIC DRUGS
PERCENTAGE OF ALL CASES

	Premed	Induction	Maintenance
None	20.3	16.9	
Barb.	8.7	76.5	4.5
Narc.	57.0	15.7	13.3
Tranq.	46.8	7.6	1.6
Antichol.	45.8	7.0	21.1
Althesin		0.5	0.04
Relax. Antag.			19.9

and 54.3 per cent during maintenance). Table 4 lists these various proportions of patients who had controlled ventilation and were intubated.

TABLE 4
PERCENT USE OF MUSCLE RELAXANTS, TRACHEAL INTUBATION,
CONTROLLED VENTILATION

	Induction	Maintenance	Postanaesthesia
Intubated	75.4	62.9	10.2
Contr. vent.	62.4	54.3	4.6
Min temp °C ($\bar{m} \pm 1SD$)		35.4 \pm 1.8	35.9 \pm 1.1

Relaxants		
	Number Cases	Per cent Cases
None	1,720	25.3
Tubocurarine (T)	156	2.3
Pancuronium (P)	537	7.9
T + P	27	0.4
Succinylcholine (S)	1,353	19.9
S + T	1,632	24.0
S + P	952	14.0
S + T + P	421	6.2

TABLE 5
PROCEDURE SITES, BLOOD LOSS AND FLUIDS ADMINISTERED

Site	Number	Per cent	Blood Loss ($m \pm 1SD$)	Fluids ($m \pm 1SD$)
Intracran	106	1.6	357 \pm 282	1875 \pm 1111
Eent	832	12.2	79 \pm 195	614 \pm 874
Hd., neck	402	5.9	213 \pm 420	1361 \pm 1441
Lung	58	0.9	434 \pm 917	1806 \pm 1710
Mjr. vess	175	2.6	885 \pm 940	3456 \pm 2637
Open hrt.	87	1.3	1099 \pm 1730	2624 \pm 2552
Cor. art.	114	1.7	1064 \pm 1208	3166 \pm 2431
Intra-abdom.	1590	23.4	442 \pm 676	2134 \pm 1911
Laparoscopy	337	5.0	87 \pm 599	676 \pm 479
Kidney	147	2.2	474 \pm 517	2229 \pm 1768
Trunk	568	8.4	171 \pm 315	918 \pm 985
Spine	135	2.0	543 \pm 740	2146 \pm 1347
Perineal	627	9.2	160 \pm 354	915 \pm 1173
Extremity	1240	18.2	177 \pm 335	1080 \pm 1001
Endoscopy	246	3.6	54 \pm 171	636 \pm 544
Other diag.	84	1.2	39 \pm 87	520 \pm 520
Other	629	9.3	198 \pm 402	1049 \pm 1163
Mean \pm 1SD			250.9 \pm 521.3*	1272.8 \pm 1466.4*

*Note that 95.2 per cent of patients had blood loss less than 1000 ml and 79.4 per cent were given 500–2500 ml of fluids.

Approximately one quarter of patients had no relaxant drug given (25.3 per cent). The most commonly prescribed relaxant was succinylcholine (60.2 per cent of all patients) either alone (19.9 per cent) or in combination with tubocurarine or pancuronium. Only 10.6 per cent of patients had a non-depolarizing muscle relaxant alone. These are listed in Table 4.

PROCEDURES, BLOOD LOSS AND FLUIDS

A total of 6,797 patients had at least one procedure, 534 had two procedures, 38 had three procedures and two had four procedures. Table 5 lists the proportions of surgical procedure sites together with mean (± 1 SD) blood loss and fluids given for each. It is notable that 4.9 per

TABLE 6
GLOBAL ANALYSIS BY AGE GROUP

	Under 10 yr	10-20 yr	Over 20 yr
Number	674	562	5561
Age (m \pm 1SD) yrs	3.48 \pm 2.53	15.81 \pm 2.79	46.23 \pm 17.39
Disease areas (%)			
Resp.	9.3	5.3	12.7
Hepatic	1.5	0.4	3.8
Circ.	5.3	4.3	26.1
Renal	3.0	5.7	6.2
CNS	4.5	5.9	6.9
Endocr.	1.2	2.1	7.0
GI	6.5	5.5	11.5
Gynec.	0.0	4.3	15.0
Ortho.	4.6	21.4	11.8
Other	24.5	19.2	14.9
Drugs			
Digoxin	0.7	0.0	3.6
Beta blk.	0.3	2.0	6.1
Diuretic	0.6	1.2	11.8
Nitrate	0.0	0.0	3.8
Bronchodil.	0.3	0.2	2.0
Smoker	1.0	12.1	27.2
Premedication			
Barbitur.	11.0	11.4	8.1
Narcotic	20.8	56.2	61.5
Tranquil.	9.8	37.4	52.2
Antichol.	38.1	45.6	46.8
Induction			
Barbitur.	33.7	74.4	81.9
Narcotic	1.8	10.4	17.9
Tranquil.	0.6	3.6	8.8
Antichol.	31.9	8.0	3.8
Maintenance			
Barbitur.	1.0	3.6	5.0
Narcotic	5.0	12.3	14.4
Tranquil.	0.6	1.4	1.8
Antichol.	5.8	12.3	23.8
Anaesthesia time (min)	72	105	131
Narcotic time (min)	52	125	128
No narcotic postop. %	65.9	55.9	45.6
Blood loss (m \pm 1SD)			
(ml)	31.7 \pm 95.3	142.1 \pm 275.0	288.5 \pm 561.3
(ml/min/m ²)	0.64 \pm 1.04	0.88 \pm 1.76	1.07 \pm 1.96
Fluids (m \pm SD)			
(ml)	130.3 \pm 301.2	893.3 \pm 960.6	1449.7 \pm 1523.2
(ml/min/m ²)	2.29 \pm 3.91	5.79 \pm 4.42	6.80 \pm 5.74

cent of cases involved major cardiovascular surgery while the most common procedure site was intra-abdominal (23.4 per cent) followed by extremity surgery (18.2 per cent). The mean blood loss was about 250 ml while mean fluid given was 1.3 litres, but there was considerable variation with procedure site and age.

DURATION OF ANAESTHESIA

The average duration of anaesthesia was 122.9 \pm 1.23 minutes with a range of 8 to 976 minutes (16.3 hours). The mean time to the first postoperative narcotic analgesic was 123.0 \pm 6.0 minutes with a range up to 150 hours.

Approximately one third of cases lasted less than one hour with 62.2 per cent lasting less than two hours, 79.6 per cent less than three hours and 89.9 per cent less than four hours. A total of 1,842 cases had narcotic given postoperatively during the first hour (27.1 per cent of all cases) with a further 585 cases having narcotic between the first and second hour postoperatively (8.6 per cent). Of the patients who received postoperative narcotic (51.6 per cent) the vast majority (89.3 per cent) received it within the first four hours after operation. This group represents 46 per cent of all patients. It is of note that 48.4 per cent of patients did not receive postoperative narcotic.

INFLUENCE OF AGE ON DISEASE AND DRUGS

The global data were examined for three age groups, less than 10 years, 10–20 years and over 20 years to determine the incidence of disease and drug combinations. These are summarized in Table 6. As might be expected, the incidence of disease was in general greater in the group over 20 years old with the exception of orthopedic disease in the group 10–20 years old (21.4 per cent). Although miscellaneous disease (other) was most frequent in the youngest group, the proportion of patients with respiratory disease was surprisingly high (9.3 per cent) in the youngest group. Renal disease was almost as common in the group 10–20 years old (5.7 per cent) as in the group over 20 years old (6.2 per cent). Current drugs were consistently higher in the group over 20 years of age. Of the anaesthetic drugs, barbiturate induction was most common in the older group (81.9 per cent) compared to the youngest group (33.7 per cent). Similar increased use of narcotic and tranquilizers was found with age. Anticholinergics were fairly uniformly used as premedication in all groups (38.1 to 46.8 per cent), whereas their use at induction was 10 times more frequent in the youngest group (31.9 per cent) compared to the group over 20 years old (3.8 per cent).

The duration of anaesthesia was least in the youngest group (72 min) and increased with age.

It is of interest that the time to postoperative narcotic was also least in the youngest group (52 min) compared to the older group (128 min). However, 65.9 per cent of the group under 10 years of age did not have postoperative narcotic compared to 45.6 per cent in the group over 20 years.

Blood loss and fluids given were predictably lower in the younger groups. It is possible that this might reflect the shorter duration of operation and smaller body size as much as the procedures done; but when blood loss and fluids were corrected for duration of operation and body surface area (m^2), the mean rate of blood loss per minute per m^2 was 40 per cent less in the youngest group compared to the over 20 year group, while fluid per min per m^2 was 66 per cent less. Despite the fact that there was a fairly large variability in all groups, as judged for example by the standard deviation around the mean values, these values do give an indication of expected blood loss and fluid requirements with increasing age.

COMPLICATIONS AND REFLEX ACTIVITY

These are described in detail in later sections; however, it is worth noting here that the overall incidence of complications and reflex activity was very low.

Of the 6,798 patients in this study, 6,247 (92 per cent) had no complications and although a total of 1,735 complications were recorded, 86 per cent of these were minor. During induction, 6,305 patients had no complications (92.7 per cent), while during maintenance and postoperatively this group amounted to 6,248 (91.9 per cent) and 6,304 (92.7 per cent) respectively. Similarly during induction, maintenance and postoperatively the proportion of patients without any reflex activity recorded was high, being 76.2, 86.3, and 68.6 per cent respectively. Of the patients showing evidence of reflex activity, most were limited to a single reflex (14.1, 9.5, and 18.9 per cent for each of these periods respectively):