NEUROLEPTANALGESICS: 2. LABORATORY EVALUATION OF COMBINATION OF ANALGESICS AND NEUROLEPTICS WITH NITROUS OXIDE*

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IN THE CONTINUING SEARCH for anaesthetic agents which produce the minimum disturbance of the normal physiology yet are clinically effective, a major impediment to a truly scientific approach, rather than empiricism, is the fact that there is still a serious lack of precise knowledge of how quite minor changes in drug molecular structure may produce such profound changes in pharmacological action, and of how different agents interact with one another.[1] However, we have found that the combination of certain drugs does complement our aim clinically and oftentimes reduces the undesirable effect of using a large dose of a single agent.[2-4]

Janssen recently introduced two groups of drugs.[5,6] One, the butyrophenones, has neuro- and psycho-sedative properties similar to those of the phenothiazines. The other (meperidine-like) has analgesic properties of great potency, and was at first thought to be without the propensity to cause addiction, but now is known to be addictive. These have been reinvestigated in detail in America during the past two years.[7-12] The expression "mineralized" has also been used to describe the state produced by injection of these drugs in combination into humans,[13] and this state is felt by some to be appropriate to the needs of a surgical operation.

Recently, also, Harris and Pierson of Winthrop-Sterling Research Institute have studied a number of compounds that are in the benzomorphan series and are rather similar to nalorphine.[14] Pentazocine (Win 20, 228) has about one-third the analgesic potency of morphine, whereas cyclazocine is at least five times as potent as morphine. The subjective effects of morphine and pentazocine appear to be similar, causing restlessness, itchiness, dizziness, grogginess, nausea, and talkativeness. Cyclazocine differs only in that it appears to be somewhat more likely to produce hallucinations. The respiratory depressant effect of both new compounds is felt to be similar to that produced by equianalgesic doses of morphine. Unfortunately, if respiratory depression is produced by these compounds, it is not antagonized by nalorphine. Cass and associates recently reported that pentazocine produces satisfactory pain relief of approximately 2 hours' duration with less side-effects than morphine.[15] Lasagna has reported the same effect with cyclazocine.[16] Of significant interest is that pentazocine appears to have no addicting properties, but this has been the unsubstantiated claim for every new analgesic except for methotrimeprazine.[17]

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Two well-known phenothiazine derivatives, methotrimeprazine (levomepromazine, Nozinan®) and promazine (Sparine®), were included in this study because they are powerful neuroleptics. Methotrimeprazine has a wide range of properties that are useful in anaesthesia, including a purported powerful analgesic effect that is said to be equivalent to that of morphine.[17-19] The properties of promazine are very similar to those of chlorpromazine, but it might be less likely to cause hypotension when given during anaesthesia.[20]

Chlorprothixene (Taractan®, Tarasan®) was used because it is also a potent neuroleptic belonging to the thioxanthene group of drugs, which is closely related in structure to the phenothiazines. In laboratory and clinical tests of this compound, we have found that it hardly differs from chlorpromazine in those properties that might be useful in anaesthesia.[21-23]

The pharmacology of the individual drugs used in this study is summarized in Figure 1.

The object of this study was to test various mixtures of these analgesic and neuroleptic drugs to determine whether they provide satisfactory anaesthetic conditions and to compare these with some mixtures which we have already tested in animals and in man.[8,9,20,23]

Material and Methods

Following preliminary experiments to devise appropriate drug mixtures, 12 combinations that appeared to be satisfactory were selected for controlled tests and were used for comparison with mixtures previously tested—thiopental-curare, fentanyl-droperidol, and thiopental-methotrimeprazine. With these, 115 experiments of the crossover type were carried out on 30 dogs weighing approximately 20 kg. (18 to 26 kg.). Groups of 5 or 10 dogs were used depending on whether the experiment was proceeding well. Each animal was premedicated with atropine 0.5 mg. and scopolamine 0.5 mg. intramuscularly, an hour before injection of the anaesthetic drugs. An intravenous infusion of 0.9 per cent saline was started in a forepaw. Succinylcholine 20 mg. was injected and, after hyperventilation with oxygen, the trachea was intubated with a cuffed endotracheal tube lubricated with 4 per cent lidocaine ointment and the tube was connected to a Takaoka respirator.[24] Pulmonary ventilation of each animal was set at 400 ml. gas/kg. body weight using a 2:1 mixture of nitrous oxide and oxygen. A Wright respirometer was interposed between the tube and the respirator to check and adjust the minute ventilation.[25]

With local infiltration anaesthesia (1.5 per cent lidocaine), plastic catheters were placed in the femoral artery and vein and threaded into the aorta and inferior vena cava in order to record blood pressures via Statham strain gauges. These were flushed as required with small amounts of heparinized saline. (No glucose was administered during any of the experiments.) After preliminary preparations were completed, the dog was placed in the lateral recumbent position on the laboratory table.

The rate of respiration was derived from the tracing using a belt-type pneumotachygraph. A rectal thermometer, urinary catheter with calibrated trap,

PHARMACOLOGICAL EFFECTS OF DRUGS WITH NEUROLEPTIC & ANALGESIC PROPERTIES

	Acute Toxicity (LD 50), mice or dogs (mpk)	Single I.V. dose / 70 kg. man (mg.)	Hypnotic sedation	Neurosedation	Psychosedation	Sensory deprivation (analgesia)	Motor deprivation (catalepsy)	Onset of effect (minutes)	Vasomotor reflex suppression	Acute tolerance*	Respiratory depression	Reversal with NALLINE or LORFAN	Potentiation of THIOPENTAL	Pulse rate	Blood pressure	Contractile force of heart	Peripheral blood flow (sympatholytic)	Hypothermia	Spasmolytic action (anticholinergic)	Antisialogogue action	Antiemetic action	Antihistaminic action	Antiadrenalin effect	Antiarrhythmic effect	Antishock effect	Antiserotonin effect	Rate of recovery	Nausea & Vomiting	Neuromuscular disturbance	Extrapyramidal seizures	Bronchial constriction	Histamine release or allergy	Behavioural upsets	Addictiveness
FENTANYL R 4263	62 m	0.1	w	w	o	p	w	4	w	s	vp	s	p	⇩	⇩	o	o	o	w	o	o	o	o	o	o	o	Fast < 1 hr.	w	p	o	p	?	?	w
MORPHINE	470 m	10	w	w	o	p	w	10	w	s	p	s	w	⇩	⇩	o	o	o	w	o	o	o	o	o	w	o	Slow 4 hrs.	p	w	o	w	p	w	p
PENTAZOCINE WIN 20228	24 m	30	w	w	o	p	?	20	w	s	p	u	p	⇩	⇩	↙	o	o	o	o	o	o	o	o	o	o	Slow 3 hrs.	w	o	o	o	o	w	?
ANILERIDINE	22 m	40	w	w	o	p	w	15	w	s	p	s	p	◻	⇩	o	o	o	o	o	o	o	o	o	o	o	Slow 3 hrs.	p	o	o	o	o	o	p
MEPERIDINE	36 m	100	w	w	o	p	w	15	w	s	p	s	w	o	⇩	o	o	o	o	o	o	o	o	o	o	o	Slow 3 hrs.	p	o	o	o	p	o	p
METHOTRIMEPRAZINE LEVOMEPROMAZINE	51 m	10	p	p	p	p	p	10	p	u	w	–	p	↗	⇩	↙	▲	vp	w	p	p	p	p	p	p	vp	v.Slow 6 hrs.	o	o	o	o	o	o	o
CHLORPROTHIXENE	25 m	10	p	p	p	o	p	15	p	u	w	–	p	◢	⇩	↙	▲	p	w	o	p	?	p	?	p	p	v.Slow 6 hrs.	w	o	o	o	o	w	o
CHLORPROMAZINE	56 m	25	w	p	p	w	p	15	p	u	w	–	p	◢	⇩	↙	▲	p	w	w	p	w	p	p	p	p	v.Slow 6 hrs.	o	o	w	o	o	w	o
DROPERIDOL R 4749	43 m	5	p	p	w	o	p	10	p	u	w	–	p	↗	⇩	↙	◻	w	w	o	vp	o	p	w	p	?	v.Slow 6 hrs.	o	w	p	o	o	w	o
THIOPENTAL	160 d	500	vp	w	vw	o	o	2	w	s	vp	–	–	↗	⇩	↙	●	o	o	o	o	o	o	w	o	o	Fast 1 hr.	w	w	o	w	o	w	o

o = none
w = weak
p = potent

*Ability to withstand repeated parenteral administration of therapeutic doses without loss of effect or deterioration of cardiorespiratory homeostasis during anaesthesia.
s = satisfactory u = unsatisfactory

FIGURE 1.

and lead 2 of the E.C.G. were attached to record body temperature, urine output, and cardiac rate and rhythm during the experiment. E.C.G., blood pressures, and respiration rate were recorded continuously and simultaneously throughout each experiment on a Grass polygraph ink recorder.

In each experiment, 20 per cent of the calculated dose was injected through the saline infusion at the beginning of the study and, after 10 minutes, the remainder was similarly injected. During preliminary experiments with some of the mixtures, it was found that the dose selected was not sufficient to provide smooth anaesthesia, so supplemental doses were given and the dose selected was revised during subsequent tests until a satisfactory one was reached and employed in the comparative experiments. Sixty minutes after the full dose was administered, artificial respiration with nitrous oxide and oxygen was discontinued and 100 per cent oxygen was insufflated into the endotracheal tube. The hind paw was pinched at 5-minute intervals until the dog responded physically; then all recording apparatus was removed, the procedure was terminated, and the dog was placed on the laboratory floor. The animals were then kept under direct observation until they were fully recovered from the anaesthetic and were able to ambulate. The occurrence of retching, vomiting, defaecation, and rate of recovery were recorded.

Arterial blood samples were drawn at the beginning and end of each anaesthetic and again when the animals became responsive. These were analysed for pH, pCO_2, and pO_2 using an Epsco Medical Blood Parameter Analyzer which uses a constant-temperature bath set at 37° C., a Metrohm constant-temperature pH electrode, a Clark platinum silver membrane-covered electrode for measuring oxygen tension, and a carbon dioxide tension electrode.[26–28] Venous blood samples were drawn before and at the end of anaesthesia to measure the haematocrit, blood sugar, blood urea nitrogen, serum potassium, SGOT, and SGPT.[29–32]

Digital tables were prepared showing a summary of the data from the tracings and laboratory procedures from each experiment. These were analysed for each group of anaesthetic tests and evaluated to determine the over-all efficacy of the anaesthetic mixture, and its probable value as a clinical anaesthetic technique.

Results

Tables I to XV show the analysed serial effects of each drug mixture on vital signs. In Tables XVI to XXX, the corresponding effects on metabolism are shown. The data in the Tables I–XXX are summarized in Tables XXXI and XXXII to show the specific *changes* that were induced by each anaesthetic mixture, so that they can be compared easily.

As previously reported, the mixture of fentanyl and droperidol (Innovar®) and the mixture of methotrimeprazine and thiopental provide satisfactory anaesthetic conditions without causing any appreciable cardiovascular or metabolic upset.[8] Similar satisfactory anaesthetic conditions were provided with all of the mixtures containing thiopental (with anileridine, fentanyl, meperidine,

TABLE I. EFFECT OF ANILERIDINE (2.5 m.p.k.) + CHLORPROTHIXENE (2 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	199		175		148	152	154	148	149	145		135
S.D.	7									12		19
Diastolic B.P. (mm. Hg)	119		84		62	65	68	67	71	67		66
S.D.	7									12		7
Mean B.P. (mm. Hg)	146		114		91	94	97	94	97	93		89
S.D.	9									14		13
Venous B.P. (mm. Hg.)	4.3		4.0		3.8	3.7	3.4	3.3	4.1	3.7		3.1
S.D.	1.0									1.6		1.1
Cardiac rate (per min.)	158		175		148	136	136	125	126	130		143
S.D.	21									44		44
Rectal temperature (°C.)	38.5		38.3		38.1	37.9	37.8	37.5	37.4	37.2		36.8

20% of total dose given | 80% of total dose given | Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE II. EFFECT OF ANILERIDINE (2.5 m.p.k.) + METHOTRIMEPRAZINE (2 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	196		162		136	135	142	145	149	149		144
S.D.	6									9		4
Diastolic B.P. (mm. Hg)	117		85		65	65	70	73	78	76		74
S.D.	13									16		5
Mean B.P. (mm. Hg)	143		111		89	88	94	97	102	100		98
S.D.	10									13		3
Venous B.P. (mm. Hg)	4.2		3.4		3.4	3.4	3.6	3.6	3.4	3.3		3.1
S.D.	0.8									1.2		0.5
Cardiac rate (per min.)	152		159		130	125	122	121	119	117		133
S.D.	43									55		42
Rectal temperature (° C.)	38.2		37.9		37.6	37.4	37.1	36.9	36.7	36.4		36.1

20% of total dose given | 80% of total dose given | Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE III. EFFECT OF ANILERIDINE (2.0 m.p.k.) + THIOPENTAL (20 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	223		213		170	172	179	176	183	189		184
S.D.	19									30		
Diastolic B.P. (mm. Hg)	129	20% of total dose given	121	80% of total dose given	89	92	94	97	100	103	Ventilation with N_2O–O_2 discontinued	96
S.D.	14									27		
Mean B.P. (mm. Hg)	161		152		116	118	122	123	127	132		125
S.D.	13									27		
Venous B.P. (mm. Hg)	4.2		3.8		4.4	4.6	4.6	4.8	4.7	4.8		4.2
S.D.	1.4									1.0		
Cardiac rate (per min.)	149		150		92	84	84	88	98	99		118
S.D.	36									47		
Rectal temperature (°C.)	38.7		38.5		38.3	38.1	37.8	37.6	37.3	37.1		36.8

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE IV. EFFECT OF FENTANYL (0.01 m.p.k.) + DROPERIDOL (0.5 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	201		188		164	161	160	161	168	168		160
S.D.	16									20		20
Diastolic B.P. (mm. Hg)	126	20% of total dose given	110	80% of total dose given	92	92	94	95	102	103	Ventilation with N_2O–O_2 discontinued	94
S.D.	9									19		12
Mean B.P. (mm. Hg)	151		136		116	115	116	118	124	125		116
S.D.	9									19		14
Venous B.P. (mm. Hg)	4.9		4.1		4.6	4.3	4.4	4.2	4.7	4.6		3.8
S.D.	1.5									1.6		1.7
Cardiac rate (per min.)	170		155		127	126	131	131	145	146		142
S.D.	33											
Rectal temperature (°C.)	38.2		37.9		37.9	37.6	37.4	37.1	36.9	36.7		36.2

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE V. EFFECT OF FENTANYL (0.02 m.p.k.) + THIOPENTAL (20 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	211		201		150	154	159	174	176	180		189
S.D.	31									39		
Diastolic B.P. (mm. Hg)	120	20% of total dose given	114	80% of total dose given	77	78	85	90	93	98	Ventilation with N_2O–O_2 discontinued	98
S.D.	14									19		
Mean B.P. (mm. Hg)	150		143		101	103	110	118	121	125		128
S.D.	16									23		
Venous B.P. (mm. Hg)	3.8		3.8		4.2	4.5	4.6	4.5	4.4	4.3		3.6
S.D.	0.8									0.8		
Cardiac rate (per min.)	147		143		87	78	85	97	104	108		145
S.D.	39									44		
Rectal temperature (° C.)	38.4		38.2		38.0	37.8	37.5	37.2	37.0	36.8		36.5

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE VI. EFFECT OF MEPERIDINE (10 m.p.k.) + CHLORPROTHIXENE (2 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	196		150		164	138	133	141	139	144		134
S.D.	26									22		31
Diastolic B.P. (mm. Hg)	113	20% of total dose given	76	80% of total dose given	95	73	69	70	70	72	Ventilation with N_2O–O_2 discontinued	74
S.D.	11									13		29
Mean B.P. (mm. Hg)	141		101		118	95	91	94	93	96		94
S.D.	15									15		26
Venous B.P. (mm. Hg)	3.8		3.6		3.4	3.4	3.2	3.2	3.4	3.0		3.2
S.D.	0.8									0.7		0.8
Cardiac rate (per min.)	155		165		154	146	167	163	158	156		197
S.D.	30									40		22
Rectal temperature (° C.)	38.3		38.2		37.9	37.6	37.4	37.0	36.7	36.4		36.2

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE VII. EFFECT OF MEPERIDINE (10 m.p.k.) + METHOTRIMEPRAZINE (2.5 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	187		161		132	137	139	137	128	130		124
S.D.	10									10		7
Diastolic B.P. (mm. Hg)	127		102		83	88	86	82	80	83		75
S.D.	5									11		8
Mean B.P. (mm. Hg)	147		122		99	104	104	100	96	99		92
S.D.	7									10		7
Venous B.P. (mm. Hg)	4.5		4 4		4.0	4.0	4.2	5.8	4.7	4.2		4.4
S.D.	0 9									0.5		0.5
Cardiac rate (per min.)	180		186		156	171	179	186	191	191		189
S.D.	24									43		49
Rectal temperature (° C.)	38.7		38.6		38.0	37.9	37.6	37.4	37.5	36.9		

20% of total dose given — 80% of total dose given — Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE VIII. EFFECT OF MEPERIDINE (10 m.p.k.) + PROMAZINE (10 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	197		151		116	117	112	115	113	115		104
S.D.	14									4		13
Diastolic B.P. (mm. Hg)	119		86		69	67	63	63	62	65		53
S.D.	13									4		7
Mean B.P. (mm. Hg)	145		108		85	83	79	80	79	82		70
S.D.	14									4		8
Venous B.P. (mm. Hg)	4.0		3.8		3.8	3.6	3.6	3.8	5.0	3.8		3.8
S.D.	1.7									0.8		0.8
Cardiac rate (per min.)	143		169		152	140	160	162	179	170		191
S.D.	28									38		34
Rectal temperature (° C.)	38.5		38.3		38.0	37.7	37.5	37.2	37.0	36.8		36.6

20% of total dose given — 80% of total dose given — Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE IX. EFFECT OF MEPERIDINE (5 m.p.k.) + THIOPENTAL (20 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg) S.D.	215 37		204		125	148	171	186	194	192 27		190
Diastolic B.P. (mm. Hg) S.D.	119 6	20% of total dose given	121	80% of total dose given	79	94	111	120	124	120 12	Ventilation with N_2O–O_2 discontinued	117
Mean B.P. (mm. Hg) S.D.	152 19		148		94	112	131	142	147	144 13		142
Venous B.P. (mm. Hg) S.D.	3.6 1.0		3.6		2.0	2.2	2.4	2.6	2.6	2.6 1.2		2.6
Cardiac rate (per min.) S.D.	141 28		148		175	166	167	167	166	162 37		168
Rectal temperature (° C.)	38.7		38.6		38 6	38 4	38 2	38.0	37.8	37.5		37.6

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE X. EFFECT OF PENTAZOCINE (5 m.p.k.) + DROPERIDOL (0.5 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg) S.D.	208 23		197		180	172	163	161	159	158 27		170
Diastolic B.P. (mm. Hg) S.D.	126 16	20% of total dose given	100	80% of total dose given	96	87	82	78	75	76 14	Ventilation with N_2O–O_2 discontinued	87
Mean B.P. (mm. Hg) S.D.	153 18		132		124	115	109	106	103	104 17		114
Venous B.P. (mm. Hg) S.D.	3.8 0.3		4 4		4.6	4.7	4.5	4.6	4.6	4.5 0.6		3.5
Cardiac rate (per min.) S.D.	144 22		117		123	123	122	123	132	130 39		151
Rectal temperature (° C)	38.9		38.6		38.4	38.3	38.2	38.2	38.2	38.0		38.2

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE XI. EFFECT OF PENTAZOCINE (5 m.p.k.) + CHLORPROTHIXENE (2 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	199		180		172	153	149	163	153	154		147
S.D.	26									17		13
Diastolic B.P. (mm. Hg)	121		87		69	71	70	83	77	76		68
S.D.	14									17		14
Mean B.P. (mm. Hg)	147		118		110	98	96	110	102	102		94
S.D.	17									16		13
Venous B.P. (mm. Hg)	4.3		4.0		4.9	4.4	4.5	4.5	4.4	4.1		3.8
S.D.	1.7									1.6		1.6
Cardiac rate (per min.)	186		227		226	210	210	192	194	199		198
S.D.	28									39		31
Rectal temperature (° C.)	37.5		37.4		37.2	37.0	36.8	36.7	36.5	36.3		36.3

20% of total dose given | 80% of total dose given | Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE XII. EFFECT OF PENTAZOCINE (5 m.p.k.) + METHOTRIMEPRAZINE (2.5 m.p.k.) ON VITAL SIGNS (MEAN OF 5 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	199		171		157	149	161	156	152	147		140
S.D.	34									20		18
Diastolic B.P. (mm. Hg)	123		81		71	70	72	72	68	67		66
S.D.	22									6		8
Mean B.P. (mm. Hg)	148		111		100	96	102	100	96	94		90
S.D.	26									5		5
Venous B.P. (mm. Hg)	5.4		5.6		5.5	5.4	5.6	5.5	5.6	5.3		4.8
S.D.	4.6									4.1		4.1
Cardiac rate (per min.)	186		196		186	182	185	182	183	179		171
S.D.	22									31		37
Rectal temperature (° C.)	38.0		37.6		37.6	37.3	37.1	36.9	36.8	36.6		36.9

20% of total dose given | 80% of total dose given | Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE XIII. EFFECT OF PENTAZOCINE (0.6 m.p.k.) + THIOPENTAL (20 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	216		222		207	206	212	213	212	213		213
S.D.	32									29		30
Diastolic B.P. (mm. Hg)	127		129		114	114	116	113	113	115		114
S.D.	18									21		22
Mean B.P. (mm. Hg)	157		160		145	145	148	147	146	148		147
S.D.	22									22		23
Venous B.P. (mm. Hg)	4.2		4.4		4.0	3.8	3.6	3.7	3.8	3.6		3.2
S.D.	1.5									1.1		1.1
Cardiac rate (per min.)	189		191		192	193	192	190	190	189		185
S.D.	16									18		16
Rectal temperature (° C.)	38.2		38.0		37.7	37.5	37.4	37.0	37.0	36.8		36.7

20% of total dose given | 80% of total dose given | Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE XIV. EFFECT OF THIOPENTAL (20 m.p.k.) + METHOTRIMEPRAZINE (0.5 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	200		138		154	158	161	162	166	166		158
S.D.	14									21		22
Diastolic B.P. (mm. Hg)	124		104		95	100	100	100	101	100		93
S.D.	13									14		15
Mean B.P. (mm. Hg)	149		116		115	120	120	121	123	122		115
S.D.	13									15		16
Venous B.P. (mm. Hg)	4.7		4.2		4.1	4.1	4.0	4.1	4.0	3.9		3.2
S.D.	1.3									1.3		1.7
Cardiac rate (per min.)	168		194		192	189	184	181	178	177		169
S.D.	21									36		43
Rectal temperature (° C.)	38.6		37.7		37.5	37.2	36.9	36.7	36.4	36.1		35.4

20% of total dose given | 80% of total dose given | Ventilation with N_2O–O_2 discontinued

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE XV

EFFECT OF THIOPENTAL (25 m.p.k.) + d'TUBOCURARINE (0.75 m.p.k.) ON VITAL SIGNS (MEAN OF 10 DOGS)

	Control		10 min.		20 min.	30 min.	40 min.	50 min.	60 min.	70 min.		Arousal
Systolic B.P. (mm. Hg)	198		173		103	121	133	139	143	151		184
S.D.	24									37		32
Diastolic B.P. (mm. Hg)	134	20% of total dose given	119	80% of total dose given	67	83	90	94	93	99	N_2O—O_2 discontinued	120
S.D.	16									27		22
Mean B.P. (mm. Hg)	155		137		79	96	104	109	110	116		141
S.D.	17									29		25
Venous B.P. (mm. Hg)	5.0		4.6		3.2	3.8	4.0	4.2	4.2	4.0	Ventilation with	3.8
S.D.	1.6									2.2		
Cardiac rate (per min.)	183		186		154	160	164	160	162	164		115
S.D.	14									22		60
Rectal temperature (° C.)	38.4		38.1		38.0	37.9	37.7	37.5	37.3	37.6		

In each experiment 20 per cent of the calculated dose was given at the beginning and the remainder was given after 10 minutes.

TABLE XVI

EFFECT OF ANILERIDINE (2.5 M.P.K.) + CHLORPROTHIXENE (2 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.43	7.35	7.23
S.D.	0.08	0.09	0.05
Arterial pCO_2 (mm. Hg)	25	27	43
S.D.	4	6	4
Plasma HCO_3^-/(mM./L.)	15.2	13.7	16.6
S.D.	0.5	0.8	1.6
Arterial pO_2 (mm. Hg)	152	153	328
S.D.	26	30	63
Venous haematocrit	46	37	35
S.D.	3	6	5
Serum potassium (mEq./L.)	4.9	4.0	
S.D.	0.4	0.6	
Blood sugar (mg./100 ml.)	127	220	
S.D.	16	42	
Blood urea nitrogen (mg./100 ml.)	12.2	11.8	
S.D.	2.9	2.8	
SGO-T units	40	37	
S.D.	5.2	6.2	
SGP-T units	27	29	
S.D.	7.0	3.5	

TABLE XVII

EFFECT OF ANILERIDINE (2.5 M.P.K.) + METHOTRIMEPRAZINE (2 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.37	7.38	7.27
S.D.	0.07	0.09	0.05
Arterial pCO_2 (mm. Hg)	28	28	42
S.D.	7	7	2
Plasma HCO_3^-/(mM./L.)	15.3	15.3	18.3
S.D.	0.7	0.9	2.0
Arterial pO_2 (mm. Hg)	143	137	298
S.D.	24	25	73
Venous haematocrit	42	36	37
S.D.	10	6	4
Serum potassium (mEq./L.)	4.9	4.1	
S.D.	0.3	0.8	
Blood sugar (mg./100 ml.)	108	138	
S.D.	16	43	
Blood urea nitrogen (mg./100 ml.)	10.6	10.0	
S.D.	0.5	0.7	
SGO-T units	38	37	
S.D.	10.2	3.7	
SGP-T units	30	29	
S.D.	12.5	14.2	

TABLE XVIII

EFFECT OF ANILERIDINE (2.0 M.P.K.) + THIOPENTAL (20 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.42	7.45	7.28
S.D.	0.05	0.07	0.05
Arterial pCO_2 (mm. Hg)	26	24	42
S.D.	4	4	5
Plasma HCO_3^- (mM./L.)	16.0	15.7	18.1
S.D.	2.2	2.0	2.7
Arterial pO_2 (mm. Hg)	187	150	347
S.D.	108	18	69
Venous haematocrit	55	43	45
S.D.	5	7	8
Serum potassium (mEq./L.)	5.1	4.2	
S.D.	0.4	0.3	
Blood sugar (mg./100 ml.)	121	133	
S.D.	20	19	
Blood urea nitrogen (mg./100 ml.)	11.5	11.5	
S.D.	2.4	2.3	
SGO-T units	44	42	
S.D.	7.3	7.0	
SGP-T units	40	42	
S.D.	7.8	8.2	

TABLE XIX

EFFECT OF FENTANYL (0.01 M.P.K.) + DROPERIDOL (0.5 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.40	7.39	7.27
S.D.	0.05	0.05	0.05
Arterial pCO_2 (mm. Hg)	25	22	33
S.D.	6	5	7
Plasma HCO_3- (mM./L.)	14.3	12.2	14.2
S.D.	2.6	2.2	2.8
Arterial pO_2 (mm. Hg)	136	139	267
S.D.	21	14	96
Venous haematocrit	40	38	37
S.D.	8	4	4
Serum potassium (mEq./L.)	4.5	3.6	
S.D.	0.4	0.4	
Blood sugar (mg./100 ml.)	138	187	
S.D.	22	41	
Blood urea nitrogen (mg./100 ml.)	11.4	10.7	
S.D.	2.5	2.4	
SGO-T units	39	44	
S.D.	6.6	6.7	
SGP-T units	37	43	
S.D.	8.7	10.4	

TABLE XX

EFFECT OF FENTANYL (0.02 M.P.K.) + THIOPENTAL (20 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.47	7.48	7.30
S.D.	0.06	0.07	0.07
Arterial pCO_2 (mm. Hg)	23	22	40
S.D.	1	3	8
Plasma HCO_3^- (mM./L.)	15.4	15.0	18.3
S.D.	1.9	1.4	2.5
Arterial pO_2 (mm. Hg)	184	201	315
S.D.	121	146	72
Venous haematocrit	53	45	50
S.D.	8	5	5
Serum potassium (mEq./L.)	5.1	4.1	
S.D.	0.4	0.4	
Blood sugar (mg./100 ml.)	112	125	
S.D.	18	18	
Blood urea nitrogen (mg./100 ml.)	12.0	11.1	
S.D.	2 7	2 3	
SGO-T units	46	45	
S.D.	18.1	19.1	
SGP-T units	41	42	
S.D.	21.7	21.6	

TABLE XXI

EFFECT OF MEPERIDINE (10 M.P.K.) + CHLORPROTHIXENE (2 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.39	7.33	7.22
S.D.	0 09	0.09	0.03
Arterial pCO_2 (mm. Hg)	28	29	41
S.D.	7	9	3
Plasma HCO_3^- (mM./L.)	15 7	13.7	15.6
S.D.	0 9	0.9	0.7
Arterial pO_2 (mm. Hg)	166	175	296
S.D.	22	25	75
Venous haematocrit	46	38	37
S.D.	4	4	5
Serum potassium (mEq./L.)	4.7	3.4	
S.D.	0.2	0.1	
Blood sugar (mg./100 ml.)	117	150	
S.D.	11	16	
Blood urea nitrogen (mg./100 ml.)	11 0	10.4	
S.D.	2 3	2.1	
SGO-T units	37	37	
S.D.	8.5	6.5	
SGP-T units	31	34	
S.D.	3.9	3.6	

TABLE XXII

EFFECT OF MEPERIDINE (10 M.P.K.) + METHOTRIMEPRAZINE (2.5 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.37	7.32	7.30
S.D.	0.04	0.09	0.06
Arterial pCO_2 (mm. Hg)	28	30	32
S.D.	5	5	5
Plasma HCO_3^- (mM./L.)	15.3	14.6	15.3
S.D.	2 6	3.0	3.3
Arterial pO_2 (mm. Hg)	149	145	239
S.D.	22	36	87
Venous haematocrit	37	35	34
S.D.	11	6	6
Serum potassium (mEq./L.)	4.8	3.5	
S.D.	0.6	0.6	
Blood sugar (mg./100 ml.)	137	201	
S.D.	24	24	
Blood urea nitrogen (mg./100 ml.)	12.5	11.5	
S.D.	1.9	1.9	
SGO-T units	36	34	
S.D.	5 0	5.3	
SGP-T units	27	29	
S.D.	3 3	4.7	

TABLE XXIII

EFFECT OF MEPERIDINE (10 M.P.K.) + PROMAZINE (10 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.41	7.34	7.24
S.D.	0.08	0.04	0.04
Arterial pCO_2 (mm. Hg)	26	28	39
S.D.	1	4	4
Plasma HCO_3^- (mM./L.)	15.9	14.0	15.5
S.D.	1 5	2.0	1 7
Arterial pO_2 (mm. Hg)	152	162	326
S.D.	16	31	55
Venous haematocrit	48	40	39
S.D.	7	5	6
Serum potassium (mEq./L.)	4.8	3.6	
S.D.	0.3	0.2	
Blood sugar (mg./100 ml.)	112	154	
S.D.	17	33	
Blood urea nitrogen (mg./100 ml.)	10	11	
S.D.	1.8	2.8	
SGO-T units	40	44	
S.D.	15.8	14.7	
SGP-T units	33	39	
S.D.	18.2	18.8	

TABLE XXIV

EFFECT OF MEPERIDINE (5 M.P.K.) + THIOPENTAL (20 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.46	7.39	7.30
S.D.	0.09	0.10	0.07
Arterial pCO_2 (mm. Hg)	26	30	41
S.D.	6	6	7
Plasma HCO_3^- (mM./L.)	17.0	17.0	18.6
S.D.	3.6	3.8	4.3
Arterial pO_2 (mm. Hg)	152	134	228
S.D.	18	30	122
Venous haematocrit	53	53	54
S.D.	6	7	6
Serum potassium (mEq./L.)	5.1	4.3	
S.D.	0.3	0.6	
Blood sugar (mg./100 ml.)	108	123	
S.D.	21	18	
Blood urea nitrogen (mg./100 ml.)	11.2	11.7	
S.D.	2.3	2.4	
SGO-T units	40	40	
S.D.	12.6	12.1	
SGP-T units	35	38	
S.D.	8.7	8.3	

TABLE XXV

EFFECT OF PENTAZOCINE (5 M.P.K.) + DROPERIDOL (0.5 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.49	7.33	7.33
S.D.	0.07	0.11	0.06
Arterial pCO_2 (mm. Hg)	22	27	26
S.D.	6	10	5
Plasma HCO_3^- (mM./L.)	15.2	13.0	13.0
S.D.	3.1	2.6	2.4
Arterial pO_2 (mm. Hg)	164	172	299
S.D.	10	15	76
Venous haematocrit	52	48	45
S.D.	5	4	4
Serum potassium (mEq./L.)	5.8	3.5	
S.D.	0.4	0.5	
Blood sugar (mg./100 ml.)	114	176	
S.D.	18	79	
Blood urea nitrogen (mg./100 ml.)	11.4	10.8	
S.D.	2.0	2.0	
SGO-T units	49	57	
S.D.	6.0	11.3	
SGP-T units	39	50	
S.D.	6.0	7.1	

TABLE XXVI

EFFECT OF PENTAZOCINE (5 M.P.K.) + CHLORPROTHIXENE (2 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.41	7.27	7.21
S.D.	0.04	0.05	0.06
Arterial pCO_2 (mm. Hg)	23	34	39
S.D.	4	5	8
Plasma HCO_3 (mM./L.)	14.8	9.9	11.0
S.D.	4.8	3.1	3.8
Arterial pO_2 (mm. Hg)	191	171	177
S.D.	70	19	35
Venous haematocrit	52	38	37
S.D.	7	5	5
Serum potassium (mEq./L.)	4.5	3.3	
S.D.	0.4	0.8	
Blood sugar (mg./100 ml.)	102	234	
S.D.	27	40	
Blood urea nitrogen (mg./100 ml.)	14.8	14.6	
S.D.	4.9	4.8	
SGO-T units	40	42	
S.D.	10.3	6.5	
SGP-T units	36	40	
S.D.	10.4	5.9	

TABLE XXVII

EFFECT OF PENTAZOCINE (5 M.P.K.) + METHOTRIMEPRAZINE (2.5 M.P.K.) ON METABOLISM (MEAN OF 5 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.42	7.31	7.19
S.D.	0.05	0.02	0.04
Arterial pCO_2 (mm. Hg)	21	22	33
S.D.	4	4	7
Plasma HCO_3^- (mM./L.)	12.6	10.4	12.0
S.D.	1.4	1.6	1.9
Arterial pO_2 (mm. Hg)	155	169	274
S.D.	23	26	53
Venous haematocrit	47	37	40
S.D.	8	4	6
Serum potassium (mEq./L.)	4.6	2.7	
S.D.	0.1	0.3	
Blood sugar (mg./100 ml.)	112	230	
S.D.	10	25	
Blood urea nitrogen (mg./100 ml.)	14.0	14.4	
S.D.	2.7	2.6	
SGO-T units	16	34	
S.D.	15.1	13.5	
SGP-T units	33	41	
S.D.	21.8	11.7	

TABLE XXVIII

EFFECT OF PENTAZOCINE (0.6 M.P.K.) + THIOPENTAL (20 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.38	7.34	7.23
S.D.	0.06	0.06	0.05
Arterial pCO_2 (mm. Hg)	23	23	36
S.D.	4	5	8
Plasma HCO_3^- (mM./L.)	12.6	11.8	13.9
S.D.	1 1	1.5	1.7
Arterial pO_2 (mm. Hg)	152	164	217
S.D.	27	33	77
Venous haematocrit	51	48	50
S.D.	4	5	5
Serum potassium (mEq./L.)	4.4	3.0	
S.D.	0.5	0.5	
Blood sugar (mg./100 ml.)	121	150	
S.D.	27	36	
Blood urea nitrogen (mg./100 ml.)	15.1	14.1	
S.D.	4.2	3.6	
SGO-T units	41	47	
S.D.	14.9	15.4	
SGP-T units	52	54	
S.D.	22.1	21 8	

TABLE XXIX

EFFECT OF THIOPENTAL (20 M.P.K.) + METHOTRIMEPRAZINE (0.5 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.40	7.41	7.25
S.D.	0.04	0.07	0.09
Arterial pCO_2 (mm. Hg)	25	25	43
S.D.	5	6	13
Plasma HCO_3^- (mM./L.)	14.7	14.3	17.2
S.D.	1 9	2.2	2.1
Arterial pO_2 (mm. Hg)	125	143	290
S.D.	30	11	21
Venous haematocrit	44	36	36
S.D.	5	5	4
Serum potassium (mEq./L.)	4.2	3.2	
S.D.	0.5	0.6	
Blood sugar (mg./100 ml.)	140	176	
S.D.	22	30	
Blood urea nitrogen (mg./100 ml.)	12.3	12.2	
S.D.	3.1	3.1	
SGO-T units	41	39	
S.D.	9.4	16.2	
SGP-T units	40	40	
S.D.	18.4	17.3	

TABLE XXX

EFFECT OF THIOPENTAL (25 M.P.K.) + *d'*TUBOCURARINE (0.75 M.P.K.) ON METABOLISM (MEAN OF 10 DOGS)

	Control	70 min.	Arousal
pH at 37.5° C.	7.30	7.30	6.96
S.D.	0.05	0.10	0.23
Arterial pCO_2 (mm. Hg)	33	30	104
S.D.	8	10	54
Plasma HCO_3^- (mM./L.)	14.7	13.3	
S.D.	2.0	3.3	
Arterial pO_2 (mm. Hg)	137	143	179
S.D.	19	21	91
Venous haematocrit	46	45	50
S.D.	7	10	14
Serum potassium (mEq./L.)	4.5	3.8	
S.D.	0.2	0.5	
Blood sugar (mg./100 ml.)	138	154	
S.D.	43	16	
Blood urea nitrogen (mg./100 ml.)	10.6	10.6	
S.D.	2.1	2.1	
SGO-T units	36	36	
S.D.	8.7	14.3	
SGP-T units	34	42	
S.D.	14.5	20.8	

pentazocine, and *d'*tubocurarine). In all of these tests, induction of anaesthesia was smooth and the dogs remained relatively quiet throughout the anaesthetic period. A few animals blinked their eyes from time to time in response to noise and some moved when blood samples were drawn, but, for the most part, the anaesthetics were considered adequate.

Among the above mixtures, the least post-anaesthetic respiratory depression was observed with the fentanyl-droperidol mixture (pCO_2 rose 8 mm. at the time of recovery) and the most depression was consistently observed when the thiopental-*d'*tubocurarine mixture (Baird's solution[2]) was used (pCO_2 rose 74 mm.). The change was remarkably consistent with the other mixtures (pCO_2 rose 13 to 18 mm.). No significant changes occurred in the blood pressure, and the heart rate usually decreased.

The mixtures containing the analgesics anileridine, meperidine, and pentazocine combined with the neuroleptics chlorprothixene, droperidol, methotrimeprazine, and promazine all proved to be unsatisfactory for one reason or another, even after considerable manipulation of the dosages in preliminary experiments. The most prominent undesirable feature was our awareness that the level of anaesthesia frequently became so light that from moment to moment we did not know whether we could hold back the administration of a supplementary dose of the mixture in order to maintain smooth anaesthesia, as evidenced by the dog blinking its eyes, gazing about, moving his limbs, chewing on the endotracheal tube, and raising the head in response to noise while, at the same time, the *mean* blood pressure was reduced at least to a level which we considered

TABLE XXXI

SUMMARY OF EFFECTS OF NEUROLEPTANALGESICS ON VITAL SIGNS

	No. of dogs	Dose (m.p.k.)	*	Blood pressure (% reduction)				Heart rate	Rect. temp. (° C.)	Urine output (ml.)	Arousal time† (min.)
				Syst.	Diast.	Mean	Venous				
Anileridine Chlorprothixene	5	2.5 2	$a-b$ $a-c$	−27 −32	−43 −44	−36 −39	−14 −28	−17 −9	−1.3 −1.7	40	94
Anileridine Methotrimeprazine	5	2.5 2	$a-b$ $a-c$	−23 −26	−43 −36	−30 −31	−21 −26	−23 −12	−1.8 −2.1	120	84
Anileridine Thiopental	10	2.0 20	$a-b$ $a-c$	−15 −17	−20 −26	−19 −24	(+14) 0	−33 −21	−1.6 −1.9	116	81
Fentanyl‡ Droperidol	10	0.01 0.5	$a-b$ $a-c$	−18 −20	−26 −25	−23 −23	−16 −22	−25 −16	−1.3 −2.0	95	76
Fentanyl Thiopental	10	0.02 20	$a-b$ $a-c$	−15 −10	−18 −18	−17 −15	(+13) −5	−27 0	−1.6 −1.9	51	84
Meperidine Chlorprothixene	5	10 2	$a-b$ $a-c$	−26 −31	−36 −34	−32 −33	−21 −15	0 (+27)	−1.9 −2.1	45	72
Meperidine Methotrimeprazine	5	10 2.5	$a-b$ $a-c$	−30 −33	−34 −40	−32 −37	−6 −2	(+6) (+5)	−1.8 −1.8	30	79
Meperidine Promazine	5	10 10	$a-b$ $a-c$	−41 −47	−45 −55	−43 −51	−5 −5	(+18) (+33)	−1.7 −1.9	25	72
Meperidine Thiopental	10	5 20	$a-b$ $a-c$	−10 −10	0 0	−6 −6	−28 −28	(+14) (+19)	−1.2 −1.1	28	76
Pentazocine Droperidol	5	5 0.5	$a-b$ $a-c$	−24 −18	−40 −30	−31 −25	(+18) −8	−10 (+5)	−0.9 −0.7	60	74
Pentazocine Chlorprothixene	5	5 2	$a-b$ $a-c$	−22 −26	−37 −43	−30 −36	−4 −11	(+6) (+6)	−1.2 −1.2	65	72
Pentazocine Methotrimeprazine	5	5 2.5	$a-b$ $a-c$	−26 −29	−45 −46	−36 −39	−2 −11	−3 −8	−1.4 −1.1	55	75
Pentazocine Thiopental	10	0.6 20	$a-b$ $a-c$	−1 −1	−9 −10	−5 −6	−14 −23	0 −2	−1.4 −1.5	140	77
Thiopental‡ Methotrimeprazine	10	20 0.5	$a-b$ $a-c$	−17 −21	−19 −25	−18 −22	−17 −32	(+5) 0	−2.5 −3.2	155	84
Thiopental *d* Tubocurarine	10	25 0.75	$a-b$ $a-c$	−23 −7	−26 −10	−25 −9	−20 −24	−10 −37	−0.8 −0.8	50	102

*$a-b$ = from beginning to end of experiment.
$a-c$ = from beginning of experiment to recovery response.

†Nitrous oxide discontinued at 70 minutes.

‡Previously reported.[8]

TABLE XXXII

SUMMARY OF EFFECTS OF NÉUROLEPTANALGESICS ON METABOLISM

	Dosage (m.p.k.)	*	pH decr.	Rise in pCO_2 (mm. Hg)	Serum K (mEq./L.)	Blood sugar (mg. %)	Bd urea N (mg. %)	SGOT (units)	SGPT (units)
Anileridine	2.5	$a-b$	0.08		−0.9	+93	−0.4	−3	+2
Chlorprothixene	2	$a-c$	0.20	+18					
Anileridine	2.5	$a-b$	0.01		−0.8	+30	−0.6	−1	−1
Methotrimeprazine	2	$a-c$	0.10	+14					
Anileridine	2.0	$a-b$	0.03		−0.9	+12	0	−2	+2
Thiopental	20	$a-c$	0.14	+16					
Fentanyl†	0.01	$a-b$	0.01		−0.9	+49	−0.7	+5	+6
Droperidol	0.5	$a-c$	0.13	+8					
Fentanyl	0.02	$a-b$	0.01		−1.0	+13	−0.9	−1	+1
Thiopental	20	$a-c$	0.17	+17					
Meperidine	10	$a-b$	0.06		−1.3	+33	−0.6	0	+3
Chlorprothixene	2	$a-c$	0.17	+13					
Meperidine	10	$a-b$	0.05		−1.3	+64	−1.0	−2	+2
Methotrimeprazine	2.5	$a-c$	0.07	+4					
Meperidine	10	$a-b$	0.07		−1.2	+42	+1.0	+4	+6
Promazine	10	$a-c$	0.17	+13					
Meperidine	5	$a-b$	0.07		−0.8	+15	+0.5	0	+3
Thiopental	20	$a-c$	0.16	+15					
Pentazocine	5	$a-b$	0.16		−2.3	+62	−0.6	+8	+11
Droperidol	0.5	$a-c$	0.16	+4					
Pentazocine	5	$a-b$	0.14		−1.2	+132	−0.2	+2	+4
Chlorprothixene	2	$a-c$	0.20	+16					
Pentazocine	5	$a-b$	0.11		−1.9	+118	−1.4	+8	+8
Methotrimeprazine	2.5	$a-c$	0.23	+11					
Pentazocine	0.6	$a-b$	0.04		−1.4	+29	−1.0	+6	+2
Thiopental	20	$a-c$	0.15	+13					
Thiopental†	20	$a-b$	0.01		−1.0	+36	−0.1	−2	0
Methotrimeprazine	0.5	$a-c$	0.15	+18					
Thiopental	25	$a-b$	0		−0.7	+16	0	0	+8
d'Tubocurarine	0.75	$a-c$	0.34	+74					

*$a-b$ = from beginning to end of experiment.
$a-c$ = from beginning of experiment to recovery response.
—†Previously reported.[8]

excessively below the control reading (>30%). Very often additional drugs had to be given to keep the animals quiet.

In none of the experiments did the electrocardiogram (lead 2) show alterations that have any significance.

Rectal temperature was invariably decreased during the course of all of the experiments, usually in excess of 1° C.

Defaecation occurred *during* a few experiments: one dog had a bloody stool during anaesthesia with anileridine-thiopental and one with meperidine-thiopental, and two dogs passed a stool during fentanyl-thiopental anaesthesia. Most of the dogs defaecated during recovery after termination of the tests. None of the dogs had diarrhoea.

None of the dogs had retching or vomiting during the recovery period. A brief red flush of the forepaw occurred when the mixture of meperidine-thiopental was injected (3 dogs).

During anaesthesia, urine output was satisfactory with all the mixtures except those containing meperidine, and the anileridine-chlorprothixene mixture (<50 ml. urine). All of the mixtures except those containing thiopental caused an appreciable rise in the blood sugar. This observation has been mentioned previously.[8] Although there was a consistent reduction in the serum potassium during anaesthesia with all the mixtures tested, only with pentazocine-droperidol was the change appreciable and probably excessive. The explanation for this change remains obscure.[8]

In all of the experiments, the changes in blood urea nitrogen, SGOT, and SGPT were negligible and of no clinical significance.

All the animals were awake within 30 minutes after the nitrous oxide was discontinued except those that received thiopental-*d*'tubocurarine. However, they were invariably unable to ambulate for a variable period of time after they were awake, extending from 30 minutes to some hours after the tests, usually because of weakness of the hind limbs. Since the femoral vessels were canulated in each dog, we were undecided as to whether the difficulty in ambulation was caused by the anaesthetic alone. All of the animals appeared to be quite normal the following day, although most of them slept on and off for several hours after each test. There did not appear to be any consistent difference in the recovery responses that could be specifically attributed to any of the mixtures.

Tests were repeated at intervals of not less than one week on the individual dogs, and with the preliminary tests most dogs had 8 anaesthetics, but none of the animals seemed to develop an aversion to the tests that might be interpreted as attributable to an unhappy psychic or sensory experience following a previous experiment.

Discussion

The evaluation of the efficacy of intravenous anaesthetic agents presents a problem in semantics which is even more complex than that related to the study of analgesics[33] and inhalation agents.[34] Quantitative and qualitative testing involves more than merely measuring the responses of a number of physiological and pharmacological parameters and then stating: "this is good, and that is not

good." When we combine two or more intravenous agents to accomplish a smooth anaesthetic state, we are certainly dealing with a far more complicated situation that at the present time can only be evaluated empirically on the basis of the occurrence of undesirable responses.[1]

In the concluding remarks of his Joseph Clover Lecture in 1954, T. C. Gray said:

> The speed of pharmacological discovery and the sudden impact of new conceptions such as hypotension and hypothermia is apt indeed to create occasional bewilderment. There is a temptation to react by developing a nostalgia for the old days when we were able to produce so much—indeed, far too much—with only one agent. If we succumb to this temptation, we talk of polypharmacy and tend to sneer perhaps a little at the 'cocktail' mentality which is developing. I have attempted to draw attention to the desirable principle, now practicable, of differential disintegration of the nervous system controlled by the anaesthetist, as opposed to the indiscriminate uncontrolled and therefore undesirable disintegration of ten years ago. This approach calls for, in American terminology, a new 'conceptual system,' a new thinking, and I would answer those who, in dismay at the effort required, ask the question 'Whither anaesthesia?' by quoting the great St. Augustine, 'Time, sirs, doth not rest, nor rolls it idly round about these senses of ours, but it worketh strange changes in the mind.'[35]

I have quoted Professor Gray on this subject for his words fit well into the current dilemma, which he foresaw.

As new and more potent analgesics and neurosedatives (neuroleptics) have been developed, we have become accustomed to the basic "cocktail" concept of Laborit and Huguenard.[36] This idea has certainly permeated the everyday practice of anaesthesia during the past decade, as most of us now use potent sedatives, muscle relaxants, analgesics, and hypnotics in combinations to accomplish satisfactory surgical anaesthesia, without a second thought, although we may attach a different name to it.[37]

There is a new question which should now be answered: Is it reasonable to combine these potent agents for intravenous administration into fixed mixtures? In clinical medicine, such a practice has not yet been officially condoned by the AMA Council of Drugs, for, as Isaac Starr has stated clearly, when two active drugs are needed, they should be given separately so that their dosages can be manipulated separately in accordance with the needs of the patient.[38] Nevertheless, some skilled anaesthetists are accustomed to using drug mixtures; they have been using them for a great many years, and they may be in the best position to test the efficacy of new drugs in combinations. Whenever their use proves unworthy of a situation, the anaesthetist can easily revert to using the specific single drug that seems to be indicated. It is only when one becomes rigid in the use of mixtures that serious problems can and do arise.

In evaluating the above series of combinations, we have kept the disadvantages of using a fixed mixture foremost in our minds and have come to the conclusion that for initiating an anaesthetic it is not inconvenient to employ a predetermined combination of drugs of evident usefulness. Thereafter, the supplementary requirements can be evaluated and judged best during the progress of a case by administering the individual compounds singly to fit the needs of the moment.

From the data reported above, it appears to us, at present, that six of the

combinations of a potent analgesic and a neuroleptic tested seem to be satisfactory for inducing clinical anaesthesia when used along with nitrous oxide. One is the fentanyl-droperidol (1:50) mixture. This mixture is the only one tested for which the term "neuroleptanalgesia" can be applied as coined by the French psychiatrist Jean Delay,[39] and first put into clinical practice by DeCastro and Mundeleer and by Nilsson.[40–42] They conceived neuroleptanalgesia as a state of central nervous system depression and sensory deprivation which is produced without the use of barbiturates or volatile anaesthetic agents.[43] The state created is one of total indifference in a *conscious* person who remains responsive to auditory stimuli and can deny awareness to painful stimuli. Since we feel, along with others, that there is no advantage to having the patient awake during a surgical operation, there is also no particular reason for eliminating the use of an ultra-short-acting barbiturate, such as thiopental. After all, this was one of the earliest of the drugs that have now come to be known as neurosedatives or neuroleptics, for, as long ago as 1936, Horsley employed thiopental for therapeutic psychotherapy (narco-analysis).[44] Since thiopental is also a potent hypnotic of relatively short action, and, in very low dosage, acts also as a neurosedative, it is not surprising that satisfactory anaesthetic conditions and a smooth recovery were provided when it was combined with potent analgesic drugs (anileridine, fentanyl, meperidine, methotrimeprazine, and pentazocine). For years now, it has been used successfully with *d*'tubocurare and/or nitrous oxide for a wide variety of surgical procedures.[2,45–48]

As the efficacy of each pair of agents is analysed, it is apparent that there is some characteristic of each which we do not especially like and there is little we can do to prevent or counteract the undesirable feature without bringing a new element into the considerations. For this reason alone, we must weigh carefully every advantage and disadvantage these drug mixtures may present before using them indiscriminately in man. We reiterate that if intravenous mixtures such as are described above come into clinical use, we must remember that once injected they are irretrievable and one cannot as easily counteract an untoward response as is possible with an inhalation agent. It is also more difficult to know what antidote to use in a given case since we are always dealing with at least two drugs with rather different properties.[1,8,9] Perhaps the most disconcerting problem that arises when such mixtures are employed in man is the possibility of psychoneurological reactions, especially when they occur several hours or days after the anaesthetic.[9]

Addiction is a problem that may only arise in a patient who needs repeated anaesthetics, and can be averted by changing the analgesic agent when subsequent operations are required. *Extrapyramidal reactions and neuromuscular dyskinesias*, although seldom recognized in animals, occur in man more often than some are willing to admit. Although these reactions can be controlled by drugs, the effect is sometimes frightening and the patient must be closely observed for at least one day after such an anaesthetic. In the case of the butyrophenones, such reactions are frequently delayed as much as two days. *Hallucinations* also occur with some of the potent analgesic drugs. Unfortunately, their occurrence cannot be studied in animals and it requires several days of close

follow-up of psychic responses of the patient for them to be revealed. We are remiss in our duty in the care of our patients if this reaction is not sought out, for the long-term effect of such a reaction may be more incapacitating to the patient than the disease for which the surgical procedure and anaesthetic was given in the first place.

Summary and Conclusions

Mixtures of several analgesic and neuroleptic drugs were devised and used in sufficient dosage to provide smooth anaesthesia in dogs. The response of the cardiorespiratory system, metabolic reactions, and postanaesthetic recovery were compared from recordings of the vital signs, blood analyses, and direct observation. These data show that the mixtures of anileridine-thiopental (1:10), fentanyl-droperidol (1:50), fentanyl-thiopental (1:1000), meperidine-thiopental (1:4), pentazocine-thiopental (1:33), and methotrimeprazine-thiopental (1:40) provide satisfactory anaesthetic conditions when used along with the inhalation of nitrous oxide and oxygen, and pulmonary ventilation is controlled during the period of anaesthesia. The thiopental-d'tubocurarine mixture would have been included if it had not caused severe post-anaesthetic respiratory depression. It is suggested that similar conditions may be reproduced clinically with all of these mixtures, but there are two major disadvantages to using such an anaesthetic technique: controllability is difficult to maintain and delayed reactions may be highly undesirable.

Résumé

On a utilisé des mélanges de plusieurs médicaments analgésiques et neuroleptiques à des doses suffisantes pour produire une anesthésie légère chez des chiens. Les effets sur le système cardio-respiratoire, les réactions métaboliques et l'évolution postanesthésique ont été comparés d'après les tracés des signes vitaux, les analyses de sang et l'observation directe. Ces données montrent que les mélanges de anilérédine–thiopental (1:10), fentanyl–dropéridol (1:50), fentanyl–thiopental (1:1000), mépéridine–thiopental (1:4), pentazocine–thiopental (1:33), méthotriméprazine–thiopental (1:40) procurent des conditions anesthésiques satisfaisantes lorsqu'ils sont combinés à une inhalation de protoxyde d'azote et d'oxygène, et que la ventilation est contrôlée durant l'anesthésie. Nous aurions ajouté le mélange thiopental-*d*-tubocurarine, mais il produit une grave dépression respiratoire postanesthésique. On est d'avis que tous ces mélanges peuvent produire cliniquement de telles conditions, mais que cette technique d'anesthésie présente deux inconvénients sérieux: il est difficile de contrôler la ventilation et il peut se produire des réactions tardives indésirables.

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