respiration is stimulated, and diuresis occurs (Lian and Charlier, 1951). During aerosol treatment over 10-15 days, 100 patients with dyspnoea of varying origins showed clinical improvement with increases in vital capacity of 100-200 c.cm. in most cases (Maulini and Barraud, 1952).

Other clinical trials of these theophylline preparations in respiratory disease have been subjective. Objective assessment has been confined to the effects of aerosol administration, and in many cases clinical improvement and increase in vital capacity could well be attributed to other factors. The compounds are widely used, and there appears to be great need for an objective appraisal of their value.

Method

The effects of these two theophylline compounds have been compared with aminophylline in patients with chronic bronchitis or asthma. Pulmonary function was assessed by measurement of the expiratory flow rate over the first 0.75 second of expiration as described by Kennedy (1953). This measure is an index of the maximum ventilatory capacity at a theoretical respiratory rate of 40 breaths a minute (hence E.F.R.⁴⁰). Each E.F.R.⁴⁰ value is the mean of the rates of six separate expirations. All drugs were given by intravenous injection, the doses used being 0.25 g. of aminophylline, 0.3 g. of neutraephylline, and 0.5 g. of etophylate. Ten patients received aminophylline and neutraephylline on two successive days, five receiving the aminophylline first and the other five the neutraephylline first. The mean of baseline readings recorded before the aminophylline (12.6 l./min., S.D. = 4.9) did not differ significantly from the mean before neutraephylline (12.6 l./min., S.D. = 4.1). Similarly, 10 other patients took part in the comparison between aminophylline and etophylate. The difference between the mean initial readings before aminophylline (14.4 l./min., S.D. = 3.4) and before etophylate (16.2 l./min., S.D. = 6.4) was not of statistical significance (standard error of difference = 1.4). Following the injections, the E.F.R.⁴⁰ was recorded at 5-minute, 10-minute, and 15-minute intervals.

Results

Comparison of Aminophylline and Neutraephylline.—Mean readings for the two drugs are shown in Table I, expressed as percentages of the initial reading before injection. It

TABLE I.—Mean E.F.R.⁴⁰ Values After Injection

	5 Minutes	10 Minutes	15 Minutes
Aminophylline	109.2% 94.5%	111.8% 91.5%	110.1% 91.5%
Neutraephylline			

will be seen that aminophylline produced consistent increase in E.F.R.⁴⁰, while the mean values following neutraephylline were less than the initial reading. The highest figures obtained by each patient have been separately calculated, and are shown in Table II, again expressed as percentages of

TABLE II.—Mean of Highest E.F.R.⁴⁰ Values Obtained After Injection

Aminophylline	116.5% (S.D. = 15.7)
Neutraephylline	97.2% (S.D. = 7.4)

the initial reading. The difference between these mean readings is of definite significance (standard error of difference = 5.5; 0.05 > P > 0.01). Tingling of the face and tongue, flushing, sweating, faintness, and hyperpnoea were frequent symptoms following an aminophylline injection, while neutraephylline produced no such sensation.

Comparison of Aminophylline with Etophylate.—Mean readings following these two injections are set out in Table III, again expressed as percentages of the initial readings. As before, a consistent increase followed aminophylline, while etophylate produced no such increase. The highest figures obtained by each patient after injection are

TABLE III.—Mean E.F.R.⁴⁰ Values After Injection

	5 Minutes	10 Minutes	15 Minutes
Aminophylline	110.4% 97.5%	113.4% 94.4%	112.6% 96.8%
Etophylate			

TABLE IV.—Mean of Highest E.F.R.⁴⁰ Values Obtained After Injection

Aminophylline	117% (S.D. = 8.7)
Etophylate	103% (S.D. = 6.9)

shown in Table IV. The difference is significant (standard error of difference = 3.5; 0.01 > P > 0.001). The injection of etophylate usually produced transient hyperpnoea of shorter duration than with aminophylline. A few patients noticed slight faintness with flushing of the face.

Conclusions

Neutraephylline and etophylate have been found to produce no increase in the expiratory flow rate of patients with chronic bronchitis and asthma, while this measurement shows improvement following aminophylline.

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COMBINATION OF CHLORPROMAZINE, PROMETHAZINE, AND PETHIDINE IN TREATMENT OF ECLAMPSIA

BY

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The main objective of all types of management of late pre-eclamptic toxæmia of pregnancy is to reduce, primarily, the maternal mortality and, secondarily, the foetal mortality. As the pathogenesis and aetiology of this disease have not yet been established, its management is still based on three time-honoured principles: prophylaxis, treatment of symptoms, and termination of the pregnancy.

However, once convulsions and/or coma set in, the woman is immediately in imminent danger of death because of grave disturbances of the central nervous system and other visceral conditions. The case becomes an urgent medical emergency, and treatment should be directed at once to the proper management of the grave medical symptoms without regard to the pregnancy. These disturbances in eclampsia manifest themselves in anoxia of the mother through convulsive spasms of the pharynx; in pulmonary oedema through impediment in venous return to the failing and decompensated heart, which is working under the strain of sudden and excessively high systolic and diastolic pressures; and sometimes in cerebral haemorrhage as a terminal stage of extreme hypertension. Added to these disturbances are impairment of liver function due to the toxæmia and anoxia, and of kidney function due to angiospasm and inadequate oxygenation.

The treatment of eclampsia, therefore, is directed to the restoration of normal functions of the maternal heart, lungs, liver, kidneys, and brain. The modern routine medical measures that are designed to restore these functions may be summed up as follows: (1) To ensure a clear airway, by direct intubation if necessary, and to maintain a 100% oxygen atmosphere; (2) sufficient glycogen replacement; (3) intravenous administration of vitamins on a body requirement basis; (4) maintenance of an adequate circulating volume of fluid under filtration pressure greater than 100 mm. Hg systolic, a wide pulse pressure, and a diastolic pressure of at least 60 mm. Hg; (5) 20% hypertonic glucose as a diuretic; (6) prompt reduction in venous return to the failing and decompensated heart which is working under the strain of excessively high systolic and diastolic pressures—this is best carried out by conduction nerve-block, which by vasodilatation produces a “bloodless phlebotomy” for as long as is necessary, and does not waste blood.

However, the all-important, all-absorbing, most disturbing symptoms which demand urgent control are the extremes of nervous excitation causing the convulsions, and the hypertension, both of which are the result of vasospasm. Every possible type of sedative and combination of sedative and hypotensive drug (anti-hypertensive) has been from time to time employed for the purpose of controlling the convulsions and reducing the hypertension.

The phenothiazine derivatives chlorpromazine and promethazine reduce tension, anxiety, and excitement (tranquillizing property), and have a potentiating effect on the activity of anaesthetics. Chlorpromazine has a place in the management of eclampsia chiefly on account of these properties. By virtue of its pharmacological effect of balancing the sympathetic and parasympathetic nervous systems it produces a “dampening” of adverse body reactions so that the metabolism of the organism is steadier, and in the event of severe stress it improves the chances of survival. Its use decreases the amount of sedative or general anaesthetic required, and it eliminates the complication of post-anaesthetic vomiting.

Chlorpromazine is a vasodepressor and vasodilator in that it reduces the pressor effect of adrenaline on the blood pressure, as a sequel to its sedative action. Large doses cause a marked fall in the blood pressure, but this action is of moderate duration. Its anticonvulsive property is fair. It is an antipyretic, and is rapidly eliminated by the body. It inhibits salivary secretion owing to its parasympatholytic effect, a property which is advantageous in the management of the unconscious eclamptic patient. Animal experiments have shown that it has no deleterious effects on the liver, heart, or kidneys. By its combination in a lytic cocktail with promethazine and pethidine (or barbiturates), a prolonged and profound sedation can be produced.

Fournel (1952) and Courvoisier *et al.* (1953) have suggested that the anti-adrenaline action of chlorpromazine and the antihistamine action of promethazine possibly afford considerable protection against the onset of traumatic shock. This protection should be of advantage in the obstetric management of the eclamptic patient.

It is well known that intra-partum eclampsia has a lower mortality than ante-partum eclampsia and that immediate delivery is associated with fewer deaths than

late delivery. The longer the convulsion-delivery interval the greater the hazard to the mother. However, the eclamptic patient is not an ideal subject for any type of operation (abdominal or vaginal) and yet the longer the condition lasts the higher is the mortality. Even if the convulsions have been controlled the patient's condition would not be improving, as only one symptom of the disease has been held in abeyance.

Present Investigation

A study of 124 consecutive unselected cases of eclampsia, treated with a lytic cocktail consisting of chlorpromazine, promethazine, and pethidine in 5% glucose, was based on the premise that chlorpromazine and promethazine reduce the hazards of traumatic shock, and that therefore termination of the pregnancy by operation (forceps or caesarean section, depending on the findings at vaginal examination) could be expedited as soon as the convulsions had been controlled. The study covered the period from November 1, 1954, to June 30, 1956 (20 months), and was conducted in the Kandang Kerbau Hospital for Women, Singapore. During the period under review, 43,206 obstetric cases were admitted into this hospital, giving an incidence of eclampsia of 1 in 348 admissions.

The eclamptic patient's urinary output, temperature, and pulse and respiratory rates are usually normal initially, and she is therefore a better risk for operation within two to three hours after the onset of convulsions than after one or more days. This question of time was thought to be an important one from the point of view of the mother's prognosis, and it was hoped that a reduction of the first convulsion-delivery interval would result in a lowering of the maternal death rate from eclampsia.

Method of Treatment.—Hudson and Siew (1956), in their preliminary report, formulated a standard of treatment using a lytic cocktail consisting of 50 mg. of chlorpromazine, 50 mg. of promethazine, and 50 mg. of pethidine in 250 ml. of 5% dextrose. The first half of this solution was allowed to flow into the vein with the drip screw wide open, and the second half was given at 200 drops a minute. When this solution had run through it was followed by a second infusion consisting of 100 mg. of chlorpromazine with 50 mg. of pethidine in 250 ml. of 5% dextrose given at a speed of 40 drops a minute. These infusions were followed by deep intramuscular injections of 100 mg. of chlorpromazine with 50 mg. of pethidine given six-hourly for three or four doses, the first intramuscular injection being initiated two hours or earlier after operation. In most of the cases reviewed in their preliminary report, this regimen of sedation alone sufficed to control the convulsions and lower the blood pressure. However, in a small number, supplementary intermittent doses of 0.1 g. of thiopentone were administered in cases where fits recurred after the infusion of the lytic cocktail. Besides adopting this regimen of sedation, the conventional modern medical measures for the treatment of eclampsia were instituted, and stress was placed on ensuring a clear airway, a high oxygen atmosphere, and the administration of 50% intravenous dextrose solution. This line of treatment was carried out in all the 124 cases studied and, so far as the procedure adopted for sedation was concerned, there was no modification.

Observations During Treatment

Within a few minutes of administration of the infusion of the lytic cocktail the patient appeared to fall into a deep sleep. This rather dramatic change was especially evident in the violently restless cases which were quickly brought under complete control. The plethoric patient assumed the pallor characteristic of chlorpromazine administration. The respiratory rate returned to normal.

The blood pressure showed an initial drop of an average of 44 mm. Hg, though in some cases this was as much as 126 mm. Hg. However, within three hours one could

Summary of 10 Deaths (All Unbooked Cases) Occurring in the 124 Cases of Eclampsia Treated

Case No.	Age	Parity	Maturity in Weeks	Highest Blood Pressure Recorded (mm. Hg)	Proteinuria	Oedema	Fits		Onset of First Fit	Time Interval between Onset of First Fit and Start of Treatment	Time Interval between Institution of Treatment and Fitness of Patient for Surgery, if Indicated	Obstetric Management	Result of Child	Cause of Death	Comments
							Before Treatment	After Treatment							
18	29	6	36	146/108	Solid	+++	4	—	Antepartum	5 hrs. 30 mins.	2 hrs.	L.S.C.S.	Alive	Incompatible blood transfusion	Blood-transfusion fatality 6th day of puerperium
34	45	3	40	174/80	"	+++	12	26	"	8 hrs. 30 mins.	2 "	Caesarean hysterectomy	"	Cerebral haemorrhage	Brought from neighbouring island 8½ hours after onset of convulsions. Deep coma. Died 5th day of puerperium
46	38	5	42	160/100	++	+++	1	—	Intra-partum	15 "	"	Spontaneous delivery	"	Heart failure	Heart failure developed 24 hours after delivery
69	29	5	40	240/140	+	+	2	—	Post-partum	10 "	"	"	"	Cerebral haemorrhage	Left-sided paraplegia. C.S.F. blood-stained. Died 19 hours after delivery
77	20	0	34	162/110	Trace	++	1	—	Ante-partum	1 hr. 45 "	2 hrs. 10 mins.	L.S.C.S.	"	Heart failure	Heart failure developed 20 hours after delivery
86	26	1	30	170/100	"	++	?	36	Post-partum	45 "	"	Spontaneous delivery	"	Status epilepticus	History of epileptic fits since childhood. Died 18 hours after delivery. Continuous uncontrollable fits from time of admission
88	41	12	41	240/140	Solid	+++	1	—	Intra-partum	10 "	13 hrs. 40 "	Amniotomy, breech delivery	"	Cerebral haemorrhage	Severe hypertensive encephalopathy, with urina. Only 1 fit. Unconscious 7 days. Kidney biopsy: marked fibrosis of glomeruli
101	24	4	41	186/132	++	+++	1	—	Post-partum	20 "	"	Spontaneous delivery	"	Heart failure	Developed acute hypertensive congestive heart failure 21 hours after delivery
103	16	1	40	100/80	++	+++	16+	—	Intra-partum	5 hrs.	30 "	Craiotomy and extraction	Still-born	Cerebral haemorrhage	Admitted in cardiac failure which responded to treatment. Cerebral haemorrhage developed 8 days after delivery
110	41	6	30	178/110	Solid	++	2+	—	Ante-partum	?	10 hrs. 40 "	Amniotomy. Spontaneous delivery	"	Heart failure	Found unconscious in her home. Admitted in cardiac failure. Died 21 hours after delivery

L.S.C.S. = Lower segment caesarean section.

expect a slight rise above the lowest level. The only precaution necessary was to nurse the patient flat in bed, instead of raising her head, should the initial fall of blood pressure reach a level lower than 100 mm. Hg.

Of the 124 cases treated, fits recurred in 43 patients (33%) after treatment had started. However, these recurrent convulsions differed materially from the usual type seen in eclampsia in that they consisted of mild twitches of the face and limbs of short duration. These atypical convulsions occurred in the oedematous patients who had been heavily sedated and whose blood pressure had dropped appreciably below the pre-treatment level. It is possible that cerebral oedema was the main cause of these manifestations of cerebral irritation, for an intravenous transfusion of 200 ml. of 50% dextrose helped considerably in the reduction of these spasms. In a few cases intermittent doses of 0.1 g. of thiopentone were introduced into the transfusion initially, until control of the spasms was effected, but this adjuvant to the sedative regimen was omitted in the later cases.

The most noteworthy point was the speed with which the patient's condition improved to a degree permitting the consideration of a method for termination of the pregnancy. In the very large majority of cases this became possible within one to four hours after starting the lytic infusion, and a vaginal examination could be carried out in order to decide whether a vaginal delivery was likely to take place in a short time, and, if this was not likely, to proceed on to caesarean section. Of the 124 cases, 34 (27.4%), or just over 1 in 4, were delivered by caesarean section. In all of them the operation was carried out within half to six hours of the beginning of treatment, except in three cases in which the caesarean section was performed after intervals of 12, 18, and 41 hours. There were three deaths among the 34 cases of caesarean section, a mortality rate of 9%, but none of the deaths could be attributed to post-operation shock or haemorrhage.

Another point, not less noteworthy, was the very small amount of general anaesthetic required for the operation and the absence of post-operation shock. In most cases nitrous oxide and oxygen with gallamine triethiodide proved very satisfactory, but in some cases, rather than risk any degree of hypoxia, minimal amounts of cyclopropane were added.

Results

Perinatal Mortality.—Thirty-three infants were lost—15 were stillborn and 18 died in the neonatal period—giving a perinatal mortality rate of 26.2% (there were two sets of twin delivery). Ten (30.3%) of these infants weighed less than 3 lb. (1,360 g.).

Maternal Mortality.—Ten patients died (see Table), giving a maternal mortality rate of 8.06%. There were four deaths from cardiac failure, four from intracranial haemorrhage, one from an improperly administered blood transfusion, and one from status epilepticus.

Summary

A study of 124 consecutive unselected cases of eclampsia treated in the Kandang Kerbau Hospital for Women, Singapore, is recorded.

A method of sedation using a combination of chlorpromazine, promethazine, and pethidine proved to be the most suitable, as patients could be quickly brought under control and prepared for delivery, thus lessening the load on the medical and nursing staff of a very busy hospital.

The results of treatment by the new method compare very favourably with those obtained prior to its introduction. In the years 1952, 1953, and 1954 (excluding November and December, 1954) a total of 188 cases of eclampsia were treated principally by the Dieckman method. The maternal mortality rate in that series was

9.6%, which is about 1.5% higher than the result obtained by the new method. The eclampsia perinatal mortality rate over the same period was 36%, which is about 10% higher than the figure for the new method of sedation, and this figure is statistically significant.

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TREATMENT OF SCHIZOPHRENIA "PACATAL" AND CHLORPROMAZINE COMPARED

BY

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Delay *et al.* (1952) first reported the use of chlorpromazine in psychiatry, and since then its value in the treatment of schizophrenia has become firmly established (Meyer, 1953; Labhardt, 1954; Lomas, 1955; Vaughan *et al.*, 1955; Boardman *et al.*, 1956).

The therapeutic success of chlorpromazine led to the trial of a host of new "tranquillizers," some of which were hailed with more enthusiasm than wisdom, and in particular to the more intensive investigation of the phenothiazine compounds. The need to find a substitute for chlorpromazine was increased by its potentially dangerous toxic effects, especially on the liver (Lomas *et al.*, 1955).

"Pacatal" (10-(N-methyl-3 piperidylmethyl)phenothiazine) is, like chlorpromazine, a phenothiazine derivative and has the graphic formula:

Nieschulz *et al.* (1954) published the first pharmacological study of the drug, and their work has since been further extended and confirmed by other workers (Nieschulz *et al.*, 1955; Kopf, 1955). In animals pacatal has similar effects to chlorpromazine in producing sedation without hypnosis and in potentiating the effects of other sedatives, hypnotics, and analgesics. It also has a similar though not so pronounced sympatholytic effect, but there is only slight antagonism to adrenaline, and, unlike chlorpromazine, pacatal has a marked depressive action on the parasympathetic nervous system. In consequence its hypotensive action is relatively weak.

Electroencephalograms in normal animals show that pacatal has a similar action to other phenothiazine derivatives, but experiments done in the Warner-Chilcott research laboratories showed that it does not block the arousal pattern, and Himwich *et al.* (1956) could demonstrate no blocking effect on the reticular formation.

Little has yet been published on the effects of pacatal in schizophrenia, but Werenberg (1955) reported improvement in 85% of 100 patients, most of them disturbed schizophrenics and nearly half of whom had been in hospital for over 20 years. Hiob and Hippus (1955) treated 65 female psychotic patients, nearly half of them diagnosed as suffering from schizophrenia: 65% were much improved and 20% were discharged. Most of them had shown no significant improvement with other physical methods of treatment including various "tranquillizers."

Bowes (1956) considered pacatal to be of most value in manic and schizo-affective psychoses. He found chlorpromazine more useful in acute schizophrenic disorders. In chronic schizophrenics he found pacatal controlled the grosser behaviour disturbances, but thought that a combination of pacatal and chlorpromazine was the treatment of choice in these cases. Jepsen (1955) thought that pacatal was effective in one out of three cases which had failed to respond to chlorpromazine and in which aggressive tendencies or paranoid symptoms prevailed.

It is the aim of this paper to compare the effects of pacatal and chlorpromazine in the treatment of the schizophrenic group of disorders.

Selection of Patients

All new admissions were included in the series when the diagnosis was schizophrenia, paraphrenia, or schizo-affective disorder and when the doctor in charge of the case considered that chlorpromazine was the treatment of choice. This excluded acute katatonic conditions where E.C.T. was indicated, schizo-affective cases where the affective disorder was predominant and consequently E.C.T. again the treatment of choice, and all those cases in which insulin was thought advisable. The results were based on 50 male and 50 female patients selected in this way. Once inclusion in the series had been decided on, patients were assigned to either the pacatal or the chlorpromazine group according to a prearranged code known only to the chief pharmacist. The order of assignment was decided by dealing out a well-shuffled pack of 25 red and 25 black cards for male and female patients.

The distribution of patients into the various diagnostic subgroups was comparable for the two groups. Over 60% of both pacatal- and chlorpromazine-treated patients were diagnosed as suffering from paraphrenia or paranoid schizophrenia, half the remainder were assigned to the katatonic subgroup, and the rest were evenly distributed between the simple schizophrenic, hebephrenic, and schizo-affective subgroups.

The age distribution for the two groups was also closely comparable. The mean age for the pacatal patients was 37.1 ± 1.5 years (males 33.8 ± 2 ; females 40.5 ± 2), while the chlorpromazine patients averaged 36.9 ± 1.5 years (males 33.4 ± 2 ; females 40.4 ± 2.1). The differences are entirely insignificant statistically.

The assessment of the duration of a mental illness is a notoriously difficult task, and is made even more so where, as in this case, the breakdown is not necessarily the first. The duration of the current attack is obviously unreliable, as it neglects the prognostic effect of previous illness. On the other hand, the duration since the first symptoms appeared may be equally unreliable. One patient in this series had a first attack 20 years ago and apparently remained perfectly well until the acute onset of her present symptoms; but if both the number of previous attacks and the duration of the illness since the first symptoms appeared are taken into account a fairly reliable guide to the comparability of the two groups can be obtained.

Table I shows the distribution of previous admissions. It will be seen that there is very little difference between the