

CLINICAL NOTES

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INCREASED CONTROL OF INSULIN COMA BY PRIOR ADMINISTRATION OF GLUCAGON : A PRELIMINARY COMMUNICATION ¹

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The hyperglycemic-glycogenolytic factor, Glucagon(1, 5), has been used extensively in our hospital(10) and elsewhere as an additional agent(2, 7, 8, 9) in Insulin Coma Therapy for rousing patients from deep coma so that they can swallow a sugar solution. Glucagon is thought to act by producing a transitory hyperglycemia due to its glycogenolytic action on the liver glycogen.

One of us (KTD) assumed that perhaps the administration of Glucagon before the insulin might reduce both the amount of insulin needed to produce coma as well as the time of onset of the coma itself. If this were found to be true, not only would it shorten the treatment time but it would also reduce some of the risks of ICT, as there is evidence that smaller doses of insulin are associated with fewer side and/or after-effects. A shorter phase 1 (during which time daily increasing doses of insulin

are given until coma ensues) is preferable because, in general, it is recognized that a decided improvement of the psychotic symptoms starts once comas are reached. It was also felt that such a procedure might be effective in producing a coma in previously coma-resistant schizophrenics.

A technique was thereby devised where 0.5 cc. of Glucagon was administered I.M. 4 hours prior to the insulin, *i.e.*, at 3:00 a.m. and 7:00 a.m., respectively. (Experiences after the period reported here show that it is preferable to use 1.0 cc. of Glucagon at 3 a.m.) This seemed a reasonable time to allow for the depletion of the liver glycogen stores and the return of the level of the blood-sugar in the venous blood to normoglycemic values.

This technique was clinically evaluated in two ways. One group of 11 patients, who were already in ICT and for whom coma doses of insulin had already been established, was switched to the Glucagon-insulin regime described, thus serving as its own control. A second group of 19 patients was started with the Glucagon-insulin treatment and compared with an earlier group of 179 patients who had been treated with insulin alone, either with single or multiple doses, excluding 30 patients treated by the Shurley-Bond technique.

Table 1 compares the established coma doses in the 11 patients of group 1 before we started to give Glucagon at 3 a.m. and after this technique had been started. Note that in all 11 cases use of Glucagon lowered the amount of insulin necessary to produce comas of equal depth. This held true whether one had used the Classical technique, the Shurley-Bond technique, or the Laqueur

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TABLE 1
Reduction of Maintenance Insulin Dose Following
Administration of 0.5 cc. Glucagon I.M. at 3 a.m.

Patient (N=11)	Technique	Pre-Glucagon Insulin Dose	Post Glucagon Insulin Dose	Difference	Reduction of Insulin Units
K. K.	Shurley-Bond	660 units	400 units	-260	39%
A. T.	Shurley-Bond	600 units	520 units	-80	13%
A. M.	Shurley-Bond	470 units	400 units	-70	15%
L. N.	Shurley-Bond	550 units	380 units	-170	31%
T. M.	Laqueur	270 units	170 units	-100	37%
J. C.	Classical	260 units	60 units	-200	77%
G. F.	Classical	330 units	220 units	-110	33%
W. Z.	Classical	130 units	70 units	-60	46%
M. C.	Classical	70 units	40 units	-30	43%
E. C.	Classical	130 units	80 units	-50	38%
M. D.	Classical	100 units	60 units	-40	40%

TABLE 2
19 Patients Started on 0.5 cc. Glucagon Prior to Insulin

Patient	Technique	Treatment Day of First Coma	Dose for First Coma	Present Coma Dose
E. D.	Laqueur	5th	30 units	40 units
H. O.	Classical	5th	65 units	60 units
F. A.	Classical	3rd	50 units	80 units
H. K.	Laqueur	3rd	60 units	80 units
T. C.	Laqueur	2nd	30 units	90 units
J. O.	Classical	2nd	30 units	60 units
L. A.	Classical	6th	110 units	90 units
M. K.	Classical	5th	90 units	50 units
R. E.	Laqueur	8th	75 units	90 units
S. H.	Classical	13th	220 units	230 units
G. B.	Laqueur	10th	160 units	150 units
A. L.	Classical	7th	130 units	110 units
E. S.	Laqueur	10th	200 units	200 units
J. T.	Laqueur	6th	100 units	100 units
T. M.	Laqueur	8th	170 units	210 units
E. C.	Classical	4th	75 units	50 units
H. F.	Laqueur	6th	140 units	140 units
K. T.	Laqueur	2nd	40 units	40 units
M. V.	Classical	4th	60 units	60 units

technique for the day to day increase until the first coma had occurred. These changes are statistically significant by the non-parametric sign test (p less than .001).

Although it is unlikely that time alone—without added Glucagon—could account for this phenomenon, one should compare these changes in patients who remain on insulin alone over similar time periods.

Table 2 presents both the insulin coma dose and the number of days before the occurrence of the first coma for the 19 patients who started ICT with the pre-treatment use of Glucagon. Note that only the Classical and Laqueur techniques are employed here

because of the possibility of dangerous overdosage if the Shurley-Bond technique were used in cases receiving Glucagon prior to insulin.

These data are compared with a previous group of 179 patients treated with insulin alone (see Table 3). Statistical analysis(3) reveals that both the mean of the dosage and the mean of the number of days to reach the first coma are significantly lower in the Glucagon group. Furthermore, the variability (F ratio) of the Glucagon group is also significantly less than that of the group treated with insulin alone.

In addition to the obvious importance of

TABLE 3
COMA DOSE REQUIRED FOR FIRST COMA
 (in Classical or Lacquer technique)

	Insulin Alone (N=179)	Glucagon-Insulin (N=19)
Mean	147.6	96.6
Standard Deviation	94.4	58.6
Difference Between Means 51.0		
t=3.36 **		
F=2.59 *		
TREATMENT DAYS TO FIRST COMA (in Classical or Lacquer technique)		
	Insulin Alone (N=179)	Glucagon-Insulin (N=19)
Mean	9.6	5.7
Standard Deviation	6.4	3.0
Difference Between Means 3.9		
t=4.64 **		
F=4.43 **		

* p less than .05.
 ** p less than .01.

the decrease in average dosage and the number of days to reach the first coma for the Glucagon-insulin form of treatment, the reduction in the variance of the dosage needed with this technique may have considerable clinical significance. This means that treatment with the Glucagon-insulin regime is more uniform, thus providing better control over the therapeutic situation.

So far, no untoward effects of Glucagon have been observed either when it was used to arouse patients from coma or in any of the 30 cases reported here. No differences in the course of coma were noted except for possibly a slight deepening in a few instances. Presently, 360 comas have been produced with Glucagon in the 19 patients of the second series, several of which are still under ICT. The daily preadministration of Glucagon tends to progressively reduce the amount of insulin needed to reach coma. In 2 patients, the doses required to produce coma after Glucagon could be reduced to as little as 25 units of insulin, one after a single injection, the other after multiple doses (after tabulation of Table 2). The reduction in insulin requirement, after Glucagon, should, therefore, be carefully gauged in the same ways as in ICT without preceding Glucagon: If coma begins before the end of the second hour and seems too deep, the dosage of the next day is reduced by 10 or more

units of insulin, but if the coma starts too late or is too mild, then an increase in dosage is given the next day.

It should be noted that Glucagon could safely be used to rouse the same patients from coma who were pre-treated with the hyperglycemic-glycogenolytic factor before insulin. It is probable that this arousal dose of Glucagon acts on glycogen reserves rebuilt by glycogenesis during the coma.

Secondary reactions are rarer and less severe in this Glucagon-treated group than had previously been observed in the cases not pre-treated with Glucagon. In one instance a patient became somnolent around 7:00 a.m. before she had received insulin, and the insulin was omitted for that day. In this case, it was possible to administer another dose of Glucagon on the following day successfully. (This patient was released after 62 comas without further unusual responses, and with a remission corresponding to a Grade 2 result(11).)

The effect of Glucagon administration on the C.N.S. appears to be different from that of hyperglycemia due to ingestion or injection of carbohydrates. Some observations point to the possibility that, because of the rebound of the regulation of carbohydrate metabolism, effects of Glucagon administration could be used to somewhat approximate the effects of subcoma insulin treatment.

CONCLUSIONS

We believe that the use of Glucagon for the arousal of patients from insulin coma and as a facilitating agent in the induction of insulin coma constitutes an important development in the modern treatment of schizophrenic psychoses, since it seems to render Sakel's treatment much easier to administer and contributes to its safety and economy.

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EFFECTS OF CHLORDIAZEPOXIDE IN SEVERELY DISTURBED OUTPATIENTS

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A series of 73 clinic patients, of whom roughly two-thirds were diagnosed as schizophrenics or as exhibiting psychotic symptoms, responded well to therapy with chlordiazepoxide (Librium)² in a study extending over a 6-months' period. This clinic acts as clearing house for the San Antonio State Hospital, screening new patients and taking over the care of others discharged from the hospital or on furlough during periods of remission. Our heavy work load makes it impossible to see patients at frequent intervals on an individual basis, and we have relied heavily on drug therapy.

Because of the large proportion of chronic and severe cases seen in this clinic the phenothiazines in variety have been the drugs of choice, despite their unpredictability and their tendency to produce side effects. In some cases these agents have apparently shortened periods of remission; more often they have failed to reduce anxiety and control undesirable behavior.

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² Trademark of Hoffmann-La Roche Inc., Nutley, N. J.

Reports of the high safety index of Librium and its specific action on anxiety led us to make the present study.

The population consisted of 31 males and 42 females, age range 16 to 73 years. The diagnoses included schizophrenic reactions 25 patients, psychoneurotic reactions 21, personality disorder 7, anxiety reaction 7, and affective reaction 5. The disturbance was often of long standing; 29 of the group had been hospitalized previously, often several times, and others had been under psychiatric treatment for many years.

The general run of patients were given Librium, 10 mg. b.i.d., or more often, t.i.d., and this amount proved acceptable as a maintenance dose in many cases. Duration of treatment ranged up to 6 months.

Seven patients were lost to follow-up. Of the 66 remaining cases, 39 were rated as showing excellent response; in 11 the results were good, in 4 fair, and in 6 poor. In 6 patients, hospitalized for electroshock therapy, no evaluation of Librium was attempted.

Thus 50 patients (75.7%) obtained good or excellent results from Librium medica-