GLUCAGON IN INSULIN COMA THERAPY[1]

Its Use in a Small Psychiatric Unit of a General Hospital

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WITH the recent laudible spread of psychiatric care and treatment to the general hospital, we felt that our experience in insulin coma treatment of hospitalized mentally-decompensated patients might be of particular interest.

Despite a great deal of controversy, a distinguished group of investigators at a recent international symposium (21) agreed in large part that insulin coma therapy still deserves a place in the modern treatment of the psychiatric patient. At any rate, although not as widely used as prior to the appearance of electric convulsive therapy and tranquilizing drugs, insulin is still administered to selected psychiatric patients by a variety of methods in many treatment settings.

Our small 15-bed private psychiatric unit has provided insulin therapy for a number of years with a staff of two regular daytime nurses, a special insulin nurse, two medical clerks (fourth-year students), and a second or third-year psychiatric resident, in addition to the attending specialists. The use of Glucagon[4] has facilitated this special treatment in 18 patients.

The Hyperglycemic-Glycogenolytic Factor (Glucagon)

Several recent reviews of Glucagon, of hyperglycemic-glycogenolytic factor, are available in the literature; however, for purposes of introductory orientation, the biochemistry and physiology of this substance will be considered briefly here.

Foa, Galansino and Pozza (7) presented an excellent general review of the literature to 1957. Van Itallie (24) was mostly concerned with the clinico-medical importance of this substance, while Berthet (2), in addition to critical clinical factors, also reviewed the physiological and biochemical aspect. Kartley and Peck (13) restricted their coverage of the literature primarily to biochemistry, and Behrens and Bromer (1), besides an excellent chemical review, also adequately reviewed the general biological effects of this hormone.

We have decided to consider Glucagon a hormone, as have Foa et al. (7), despite the controversy in the literature (2, 24) for a number of reasons. After its initial discovery (19), isolation (12), and naming as a distinct entity (9) by Murlin and his group in 1923 and 1924, further definitive experimental work was not forthcoming for several years. In 1953, after a number of attempts and failures by other workers, Glucagon was chemically isolated and purified by Staub, Sinn and Behrens (23) in the Lilly Laboratories. Its chemical structure was described in 1956 by the same workers, Bromer et al. (4), who found a zinc-poor polypeptide with 29 component amino acids (different from insulin). Glucagon has been present in all vertebrates studied thus far (2), and, with two exceptions, appears to be secreted mainly by the alpha cells of the pancreas (13). Insulin administration increases (stimulates) the elaboration and release of Glucagon by the pancreas (16), and it is dependent upon the permissive effect of adrenocorticosteroids for its glycogenolytic action (1). A substance indistinguishable from Glucagon chemically and physiologically has been demonstrated in the blood of man and dog by Makman, Makman and Sutherland (17).

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Plasma inactivates Glucagon *in vitro*, but, interestingly, not insulin, apparently through hydrolysis by the proteolytic enzyme plasmin (18). The basis, then, of rejecting the hormonal character of Glucagon rests almost entirely upon the lack of clear-cut clinical syndromes of its over- and/or under-production (2, 7, 24).

Three principle actions of Glucagon have been worked out to date. The most important is the hyperglycemic effect which results from the activation of liver phosphorylase and consequent stimulation of glycogenolysis within the liver. This, significantly, comes nearest to being a complete description of the ultimate mode of action of any hormone in the biochemical literature (18). This activation of phosphorylase is, of course, similar to that of epinephrine, but, in contrast, is not blocked by ergotamine. As stated above, principal production of Glucagon is in the pancreas, with the stomach and duodenum (but no other organs) also implicated in some species. This, of course, provides for the high levels of this rather quickly inactivated material which can then be poured into the portal circulation and, thence, into the liver. A peripheral action of Glucagon is not yet "clear-cut" (2); in fact, Randle (20) found no effect, except from insulin contaminants, upon the glucose uptake of isolated rat diaphragm.

A second possible action of Glucagon is upon the renal tubule. Administration of the hormone causes an increase in sodium, potassium, chloride, phosphate and radioactive iodine excretion from the kidney (13). Foa et al. (7), feel Glucagon might be of considerable importance in the control of bodily levels of potassium, but admit that further work in this area needs to be done.

The third principal action is the inhibition of gastric motility and secretion which persist, in distinction to the effects of insulin on the stomach after denervation (13).

Psychiatric Uses of Glucagon in Insulin Coma Therapy

Traditionally, the hypoglycemic coma induced by the insulin has been terminated by the administration of glucose solution intravenously, or by gastric gavage. The technical difficulties of these methods are well known to those who have worked directly with them; however, in 1957, Schulman and Greben (22) first reported the use of Glucagon in the termination of insulin coma in a carefully conceived and executed study. It was given I.V. or I.M. (the former considered better by these workers), proved to have no adverse general or local effects, and the dosage (most effective 0.2 mg/kg body weight) was not dependent upon the amount of insulin which had been administered. The average awakening time was about 15 minutes (criterion: to the time glucose solution could be taken orally) in the 141 terminations of 11 patients reported. The responsiveness to Glucagon, in general, increased during the course of treatment. The average blood sugar levels were 15 mg% before Glucagon and a maximum of 33.6 mg% afterward. The failures (criterion: more than 30 minutes for arousal) which occurred were more frequent after spontaneous convulsions.

Esquibel, Kurland and Mendelsohn (6) gave 5 mg of Glucagon I.M. to 13 patients (545 trials) in the third or fourth stages of coma (10) with comfortably good results. Again, the greatest number of failures (four out of a total of seven) were in patients who had had spontaneous convulsions. These investigators felt that intramuscular administration was as good or better than intravenous or subcutaneous routes, and found that hyaluronidase did not augment the Glucagon-effect. Braun and Parker (3) terminated 375 comas (which they tried to limit to Stage II, but also included Stages III and IV) in 15 schizophrenics, and were able to reduce the dosage to 2.5 mg after initially using up to 5 mg. The Glucagon dosage was not related to the patient's weight or to the amount of insulin received.

Recent reports from the foreign literature (8, 11) will not be reviewed here but indicate a widespread use of Glucagon in the termination of insulin coma.

The administration of Glucagon, then, would seem to be an effective method for the termination of insulin-induced hypoglycemic coma. However, a few practical and theoretical possible limitations should be mentioned here. The

duration of action (raising of blood sugar levels) is short; therefore, the time in which a patient can respond and take oral fluids is not lengthy, so they must be administered appropriately. The effect of Glucagon on electrolyte excretion, as mentioned above, may be of significance, especially with regard to potassium, in some patients. This probably can be easily controlled with adequate dietary intake, and, if necessary, supplementary feeding of the appropriate substance. The addition of potassium chloride to the medical regimen of all insulin patients is routine in our unit. The majority of insulin patients eat well so that the increased nitrogen loss in the urine (13) is probably not of importance. The adrenocortical activation (15) is, in all likelihood, not of sufficient extent and duration to be of great significance. Alterations in gastric motility and secretion might influence rapidity of uptake of oral glucose, but has not been a deterring factor in our experience, and actually has been helpful in possibly decreasing nausea. Although untoward allergic and other reactions were not encountered in our work, hypotension has been reported by Carleton, Greben and Schulman (5).

Finally, a recent paper from Best's Laboratory (14) adds one possibly important consideration. The chronic administration of Glucagon (1 mg b.i.d.) to 9 newborn rabbits for five to six months resulted in the appearance of two reaction types. Five of these animals developed diabetes (blood sugar above 300 mgs/100 ml and 15 to 45 gm sugar spillage in urine per day) which persisted in all but one of the group (spontaneous recovery in 20 days in that one). When 3 of these were killed and autopsied, demonstrable atrophy of the pancreatic alpha cells was seen. The remaining 4 rabbits developed only transient hyperglycemia to Glucagon injection and autopsies of 2 showed beta cell hypertrophy in the pancreas. Admittedly, more work needs to be done on this problem; however, these findings constitute a necessity for caution.

Results

From April to October, 1959 (work still in progress), 20 patients have been treated 315 times, using Glucagon.

Dosage - The range was 2 to 5 mg; 70% being given 5 mg. intramuscularly. (Only one patient needed the additional I.V. glucose.)

Time - For reaction, sufficient for the patient to drink glucose, varied from 10 to 25 minutes; 84% reacted in 15 to 20 minutes.

The median insulin dose for coma was 110 units, the range being 40 to 280 units.

In 130 treatments, 115, or 89%, were in Stage III and IV when terminated.

Blood Glucose, measured in 15 patients, was within a range of 0 to 23 mg%, with a mean of 15 mg% before Glucagon was given. After Glucagon, when the patient was sufficiently awake to drink, the range was 21 to 70 mg%, with a mean of 44 mg%. The elevation of blood sugar after Glucagon was 18 to 52 mg%; the median elevation was 32 mg%.

Blood Phosphorus (normal 2.5 - 4 mg%) before Glucagon in 6 patients was 2.05 to 6.3 mg; after injection, the range was from 1.33 to 3.35 mg. The changes before and after injection in 4 cases were +0.3, +0.33, +0.5 mg and −3.05 mg.

Blood Potassium (normal 4 to 5 meq) ranged from 3.34 to 4.56 meq; after, from 3.55 to 5.36 meq. The range of change was −0.64 to +1.36 meq.

Blood Sodium (normal 141 to 150 meq) showed very little change before and after, all in the normal range. In 9 patients, range before was 135 to 153 meq; after, 133 to 150 meq.

No cases of protracted coma resulted. One patient had a delayed shock and was awakened by additional Glucagon. One patient required I.V. glucose because of nausea.

Conclusion and Summary

Glucagon therapy was utilized in 20 patients for a total of 315 insulin coma treatments.

Although the exact nature of Glucagon is not known, it appears to be a hormone. It has definite hyperglycemic qualities, possibly works on the renal tubule, and inhibits gastric motility and secretion.

In bringing patients out of insulin coma, it awakens the patient sufficiently in 15 to 20 minutes so that he can drink glucose, making intravenous glucose injection or gavage unnecessary. No cases of protracted coma occurred. Delayed insulin shock can be treated easily by a nurse by giving I.M. Glucagon for oral feeding.

Some studies on the blood chemistry, before and after Glucagon was given, are reported. There are many problems which need to be worked out with this important chemical as a research agent, and further clinical application.

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