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# Correlates of Outcome Following Acute Glutethimide Overdosage

Glutethimide was introduced as a hypnotic agent in the United States in the mid-1950s. Shortly thereafter it became evident that overdosage with glutethimide could readily produce serious and fatal intoxication [*1-3*]. Numerous subsequent studies demonstrate that the sleep-inducing efficacy of glutethimide is no greater than that of many other drugs, including some that are clearly safer [*4-13*]. Furthermore, glutethimide continues to be a popular agent of self-poisoning, with an associated high morbidity and mortality [*11,13-23*]. Despite the obvious hazards and disadvantages of glutethimide, it is still widely used in clinical practice. An estimated 2.7 million prescriptions for glutethimide were dispensed at American retail pharmacies in 1975.

Central nervous system (CNS) depression following glutethimide overdosage is unpredictable in severity and may fluctuate over time [*2,3,17,23,24*]. There is a need to identify factors that may predict or correlate with subsequent development of serious intoxication so that the use of expensive intensive care and monitoring facilities can be appropriately allocated to those at risk. Previous studies focusing on the ingested dose of glutethimide or the glutethimide blood concentration as predictors or correlates of morbidity have yielded equivocal results [*21-23*]. The present investigation assessed the value of several potential predictors of morbidity and mortality following acute glutethimide overdosage.

## Methods

The Massachusetts General Hospital is a 1089-bed general medical center. For all patients admitted between 1962 and 1975, diagnoses were coded descriptively and numerically and stored on magnetic tape. Patients whose diagnoses were consistent with self-inflicted injury, deliberate or accidental self-poisoning, or attempted suicide were identified by computer. A research nurse (M. D. A. or B. J. N.) reviewed the medical records of all such patients 15 years of age or more. As in previous studies [*13*], pertinent data were recorded on a standardized form, and the excerpted clinical summaries were used to prepare this report. The severity of CNS depression was rated by the research nurse using the following system of Matthew and Lawson [*25*]: Grade 1, drowsy but response to verbal stimulation; Grade 2, response to mild painful stimulation; Grade 3, minimum response to maximum painful stimulation; and Grade 4, no response to maximum painful stimulation.

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The variables available for mathematical analysis were divided into two categories. The first included those that relate to clinical outcome: survival, deepest coma grade, duration of hospitalization, the need for intubation or assisted ventilation, and the development of hypotension. A second set of variables included factors available on admission that might be subsequent predictors of clinical outcome: age, sex, dose of glutethimide ingested, and coingestion of ethanol, barbiturates, or other drugs. Also included in this category was the plasma concentration of intact glutethimide, determined by the method of Rieder and Zervas [*26*]. When more than one level was measured in the same patient, the highest concentration was used in the statistical analyses.

The pairwise interrelation of all these variables was determined by linear regression analysis. However, since many of the variables are in themselves correlated, the relation of each of the five outcome measures to the seven potential predictors was determined by multiple regression analysis [*27,28*].

## Results

The number of medical admissions to Massachusetts General Hospital between 1962 and 1975 was 97 994 (average, 7538 per year). A total of 773 admissions (0.8% of the total), involving 701 patients, was attributable to accidental or deliberate overdosage with a psychotherapeutic drug. This total does not include 35 admissions for which the hospital record was lost, confidential, or otherwise unavailable for administrative reasons. Analysis of cases treated in the emergency room and discharged without hospital admission was not possible since computerized records of the diagnoses of such patients are not available.

Review of these records revealed 63 cases for which clinical findings or toxicologic analyses indicated that glutethimide was among the drugs ingested (Table 1). Their mean

TABLE 1—*Patient characteristics and consequences of glutethimide overdosage.*

| Characteristic | Cases for Which Information Was Available, *n* | Values[a] | Range |
|---|---|---|---|
| Age, years | 63 | 34.0 (±1.9) | 15-84 |
| Sex (m/f) | 63 | 24/39 | ... |
| Survival | 63 | ... | ... |
| Died | ... | 6 | ... |
| Survived | ... | 55 | ... |
| Transferred to another hospital | ... | 2 | ... |
| Glutethimide dose, g | 34 | 7.7 (±0.7) | 2.8-15.0 |
| Highest glutethimide plasma concentration, μg/ml | 35 | 20.1(±2.9) | 2.0-63.0 |
| Duration of hospitalization among survivors, days | 55 | 5.2 (±1.0) | 1-52 |
| Coingestion of ethanol (yes/no) | 62 | 6/56 | ... |
| Coingestion of barbiturates (yes/no) | 63 | 28/35 | ... |
| Coingestion of other drugs (excluding ethanol and barbiturates) (yes/no) | 62 | 18/44 | ... |
| Hypotension [systolic blood pressure ≤ 12 kPa (90 mm Hg)] (yes/no) | 62 | 20/42 | ... |
| Required intubation (yes/no) | 63 | 37/26 | ... |

[a]Mean (± standard error), or actual values, given as appropriate.

age was 34 years; the age range was 15 to 84 years, but only 3 patients (aged 71, 80, and 84 years) were older than 60. Thirty-nine of the 63 individuals (62%) were female. Six patients died, and two were transferred to another hospital for hemodialysis. The quantity of glutethimide ingested averaged 7.7 g, and the maximum plasma glutethimide concentration averaged 20.1 $\mu$g/ml. Intubation was required in 59% of patients, and at least one episode of hypotension developed in 32%.

Clinical characteristics of the six fatal cases are given in Table 2. The interval between admission and death ranged from 18 h to 9 days. Death resulted from complications such as intractable hypotension, respiratory failure or infection, impairment of temperature regulation, or some combination of these. The six fatal cases included all three of the elderly patients; five of the six fatalities also ingested barbiturates.

Table 3 indicates the relationships among all variables included in the study. Although most of these correlations did not approach statistical significance, survival and age were highly correlated ($r = -0.54$, $P < 0.001$), consistent with the observations in Table 2. Not unexpectedly, the deepest coma grade was highly correlated with the need for intubation ($r = 0.66$, $P < 0.001$), and was also associated with the development of hypotension ($r = 0.49$, $P < 0.001$), the dose of glutethimide ($r = 0.43$, $P < 0.05$), and with the highest plasma glutethimide level ($r = 0.36$, $P < 0.05$). Figures 1 and 2 show the relation between deepest coma grade, the maximum plasma glutethimide concentration, and the estimated ingested dose, with cases subdivided according to whether barbiturates were coingested. A concentration of 30 $\mu$g/ml or greater was always associated with a coma grade in excess of 2, and a dose 10 g or greater was associated with a coma grade of 3 or 4 in 11 of 13 cases. Thus the plasma glutethimide concentration or the estimated ingested dose, or both, do have some value as predictors of serious CNS depression. On the other hand, the converse is not always true. Deep coma is not necessarily associated with high plasma levels or large ingested doses, in part because many individuals with Grade 3 or 4 CNS depression despite relatively low doses or low glutethimide plasma concentrations also had ingested barbiturates (Figs. 1 and 2).

Multiple regression analysis allowed assessment of the relative contributions of each of the independent variables to a given measure of clinical outcome (Table 4). The relative magnitudes of the standardized regression coefficients correspond to the relative importance of each independent variable. The value of multiple $R^2$ indicates the fraction of the total amount of variability in the dependent factor that is collectively explained by the independent factors. As suggested by Table 2 and by the simple correlation coefficients (Table 3), age was the most important determinant of survival. Sex and coingestion of other drugs had a lesser influence, while the other three variables had very little or no influence. Only 39% of the total variability was explained by the independent factors taken together. In contrast, glutethimide dose, plasma level, and coingestion of barbiturates were the major determinants of coma grade; other independent variables had little or no influence. Forty percent of the overall variability was explained. Glutethimide dose also was the major determinant of the need for intubation; plasma glutethimide level and coingestion of barbiturates explained small amounts of variability, while the other variables had very little influence. Again, less than half of the overall variability was explained by the independent factors. The development of hypotension and the duration of hospitalization were not well explained by the combination of the independent factors; only 21 and 10%, respectively, of the overall variability was explained.

## Discussion

The present analysis of the course and consequences of glutethimide overdosage in a series of 63 patients confirms that serious and fatal poisoning commonly results from ingestion of this compound. Six of 63 patients died, and another two required transfer

TABLE 2—*Clinical summary of six fatal cases.*

| Case | Age/Sex | Glutethimide Dose, g | Highest Plasma Glutethimide Level, μg/ml | Other Drugs Ingested | Complications | Interval Between Admission and Death |
|---|---|---|---|---|---|---|
| 1 | 80/m | unknown | 18 | barbiturate | hypotension; hypothermia; respiratory failure | 3 days |
| 2 | 71/f | 13.5 | 26 | barbiturate | hypotension; respiratory failure | 23 h |
| 3 | 17/m | unknown | unknown | barbiturate | hypotension; pulmonary infection; hyperthermia | 18 h |
| 4 | 84/m | 5.0 | unknown | barbiturate | hypotension; respiratory failure; pulmonary edema | 36 h |
| 5 | 59/m | unknown | 22 | barbiturate | hypotension; respiratory failure; hyperthermia; renal failure; grand mal seizures | 9 days |
| 6 | 41/f | unknown | unknown | none | respiratory failure; pulmonary edema; renal failure; hypotension; hyperthermia | 51 h |

TABLE 3—*Correlation coefficients.*

| Variable | Sex[a] | Survival[b] | Deepest Coma Grade | Glutethimide Dose | Highest Plasma Glutethimide Level | Coingestion of Ethanol[c] | Coingestion of Barbiturates[c] | Coingestion of Other Drugs[c] | Intubation[c] | Hypotension[c] | Duration of Hospitalization |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 0.003 | −0.537 | 0.213 | 0.246 | −0.022 | 0.032 | 0.231 | −0.104 | 0.255 | 0.268 | 0.112 |
| Sex[a] | ... | −0.197 | 0.055 | 0.011 | 0.113 | −0.138 | 0.153 | 0.148 | 0.126 | 0.113 | 0.126 |
| Survival[b] | ... | ... | −0.356 | −0.125 | −0.066 | 0.111 | −0.248 | 0.210 | 0.285 | −0.473 | ... |
| Deepest coma grade | ... | ... | ... | 0.431 | 0.357 | −0.157 | 0.270 | 0.110 | 0.659 | 0.493 | 0.390 |
| Glutethimide dose | ... | ... | ... | ... | 0.040 | −0.180 | −0.088 | 0.397 | 0.482 | 0.120 | −0.138 |
| Highest plasma glutethimide level | ... | ... | ... | ... | ... | −0.282 | −0.134 | −0.138 | 0.305 | 0.370 | 0.018 |
| Coingestion of ethanol[c] | ... | ... | ... | ... | ... | ... | −0.287 | −0.205 | −0.176 | 0.004 | −0.068 |
| Coingestion of barbiturates[c] | ... | ... | ... | ... | ... | ... | ... | 0.062 | 0.231 | −0.002 | 0.206 |
| Coingestion of other drugs[c] | ... | ... | ... | ... | ... | ... | ... | ... | 0.112 | −0.260 | 0.035 |
| Intubation[c] | ... | ... | ... | ... | ... | ... | ... | ... | ... | 0.377 | 0.367 |
| Hypotension[c] | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | 0.338 |

[a]Designated as 1 for male, 0 for female.
[b]Designated as 1 for survival, 0 for death (two patients transferred to another institution were not rated).
[c]Designated as 1 if present, 0 if absent.

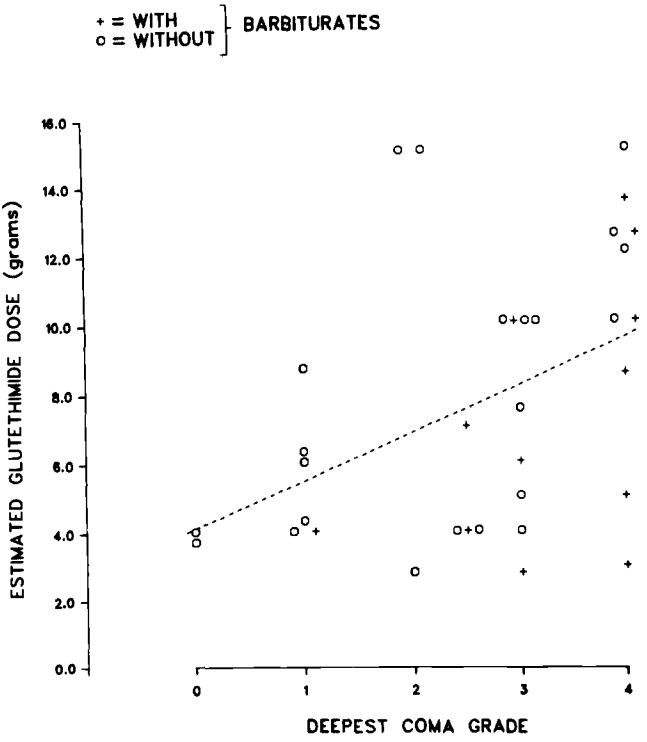


FIG. 1—*Relation of estimated ingested dose of glutethimide to deepest level of CNS depression, with cases divided according to whether or not barbiturates were coingested. Dashed line was determined by least-squares regression analysis* ($r = 0.43$, $P < 0.05$).

to another hospital for hemodialysis. Major complications, such as hypotension or the need for assisted ventilation, were common.

Despite the high percentage of serious intoxications, there was considerable variation among individuals in the clinical consequences of glutethimide overdosage. The ability to identify those individuals at risk of developing serious or life-threatening complications, based on information available on admission, would be of considerable value to clinicians, since facilities for intensive care and monitoring could be most appropriately allocated. The present study used multiple regression analysis to assess several clinical and epidemiologic factors (independent variables) generally available on admission in relation to measures of clinical outcome. This approach allowed estimation of the relative importance of each independent factor, as well as their overall contribution to explaining the variability in the outcome measures.

Survival clearly is the most important measure of outcome. In our sample, only 39% of the variability in survival was explained by the seven independent factors, but age by itself was the most important of the identifiable variables. This was confirmed by inspection of the characteristics of the six fatal cases. The six fatalities included all three patients who were older than 60 years, aged 71, 80, and 84 years. Thus age appears to be a major determinant of mortality following glutethimide overdosage, regardless of other characteristics of the patient or the circumstances of ingestion. The findings might be due to an intrinsically increased sensitivity to CNS depressant drugs among the elderly [*29,30*], to age-related pharmacokinetic changes leading to less efficient drug elimination [*31-33*], to disease processes occurring in old age that could exaggerate depressant drug effects, or to some combination of these factors. In any case the results strongly suggest that

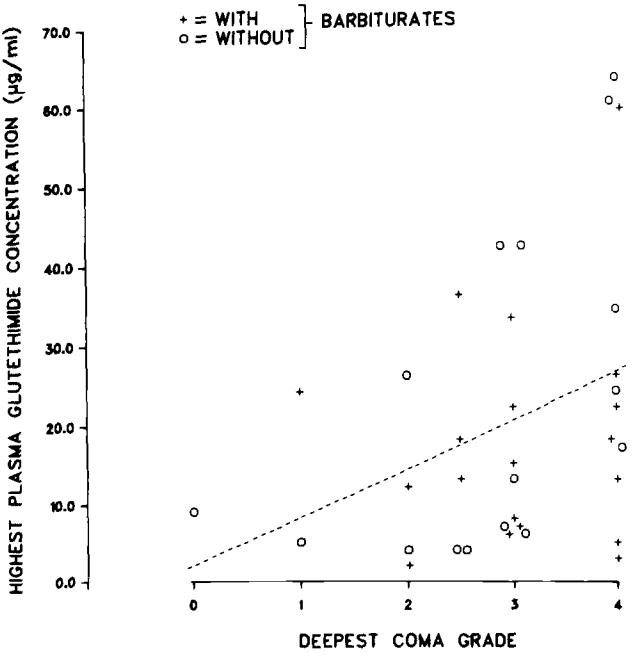


FIG. 2—*Relation of highest plasma glutethimide concentration to deepest level of CNS depression, with cases subdivided according to whether or not barbiturates were coingested. Dashed line was determined by least-squares regression analysis* ($r = 0.36$, $P < 0.05$).

elderly patients should receive priority for intensive monitoring following glutethimide overdosage.

The seven independent variables collectively explained 40 to 42% of variation in the degree of CNS depression (as measured by coma grade) and in the need for intubation. Glutethimide dose was the most important such factor in both of these measures of clinical outcome; plasma glutethimide level and coingestion of barbiturates also contributed substantially. We should emphasize that the assay method used for quantitation of plasma glutethimide measured only the intact compound, and not a hydroxylated metabolite (4-hydroxyglutethimide) [*34-37*]. Concentrations of this metabolite may correlate better with clinical manifestations of overdosage than concentrations of the unchanged drug [*38*]. Routine measurement of this metabolite might allow more reliable prediction of clinical consequences of overdosage. However, quantitation of 4-hydroxyglutethimide requires more sophisticated analytic techniques than are available in most medical centers.

Although neither glutethimide dose, plasma level, nor coingestion of barbiturates appeared to influence eventual survival, the apparent relation of these factors to two important clinical consequences of overdose suggest that estimation of the ingested dose, measurement of plasma glutethimide concentration, and assessment of whether barbiturates also were coingested constitute important aspects of early evaluation of such patients.

## Summary

Potential predictors of outcome following acute glutethimide overdosage were assessed in 63 patients hospitalized with this diagnosis at a large urban medical center between

TABLE 4—*Correlates of outcome in glutethimide overdosage: multiple regression analysis.*

| Dependent Variable | Standardized Regression Coefficients for Independent Variables | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Age | Sex[a] | Glutethimide Dose | Highest Plasma Glutethimide Level | Coingestion of Barbiturates[b] | Coingestion of Ethanol[b] | Coingestion of Other Drugs[b] | Multiple $R^2$ |
| Survival[c] | −0.46 | −0.20 | −0.10 | 0.0 | −0.11 | 0.10 | 0.26 | 0.39 |
| Coma grade | −0.05 | 0.0 | 0.49 | 0.37 | 0.37 | 0.16 | 0.0 | 0.40 |
| Duration of hospitalization | 0.17 | 0.10 | −0.21 | −0.13 | 0.10 | −0.10 | 0.07 | 0.10 |
| Intubation[b] | 0.0 | 0.07 | 0.54 | 0.34 | 0.31 | 0.12 | −0.04 | 0.42 |
| Hypotension[b] | 0.16 | 0.15 | 0.20 | 0.19 | 0.0 | 0.05 | −0.30 | 0.21 |

[a]Designated as 1 for male, 0 for female.
[b]Designated as 1 if present, 0 if absent.
[c]Designated as 1 for survival, 0 for death (two patients who transferred to another institution were not rated).

1962 and 1975. Their mean age was 34 years (range, 15 to 84 years) and 62% were female. Assisted ventilation was required in 59% of cases, and 32% developed hypotension. Six patients died, including all three aged 60 years or older. Multiple regression analysis confirmed that age was the major identifiable determinant of survival, regardless of other factors. Among identifiable determinants of coma grade, glutethimide dose, glutethimide plasma concentration, and coingestion of barbiturates were the most important. An ingested dose of 10 g or more, or a plasma concentration exceeding 30 μg/ml, was almost always associated with deep coma. However, a relatively small ingested dose or a low plasma level by no means ruled out development of serious intoxication, particularly in those patients who also ingested barbiturates. Thus elderly individuals are at high risk for fatal outcome following glutethimide overdosage and should receive priority for intensive care and monitoring. Glutethimide dose, plasma concentration, and history of coingestion of barbiturates are of value in predicting development of deep coma. These items of information should be obtained on admission whenever possible.

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