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DEVELOPMENT OF CASE HISTORIES INVOLVING DRUG THERAPY

CASE HISTORY

Please read the following hypothetical case history:

A 45-year-old, married, Negro male, construction worker was seen in a physician's office with complaints of occasional, nonspecific, dull-aching, occipital and parietal headaches and fatigue for the past five-six years. He had "always been a nervous person" and seemed rather labile emotionally. He had become increasingly nervous after the recent death of his only child. He was on no medication. Family history revealed that his father died at age 62 of hypertension and a cerebrovascular accident; one brother was said to be hypertensive. Further past medical history and review of systems were noncontributory.

On physical examination, the patient was a moderately obese, stocky, anxious man in no acute distress. Height was 69 inches; weight, 200 pounds. Blood pressure initially was 180/100 in both arms (standing, sitting, and lying down) and 190/100 in both legs (lying down). Arterial pulsations were equal and full in all extremities. No bruits were detectable. The eye grounds were normal bilaterally; neck veins were not distended. The thyroid was not palpable. The heart was not enlarged to percussion; heart rate was 90 beats per minute and regular. No murmurs were heard. Examination of the lungs, abdomen, and extremities was normal. Neurological examination was within normal limits. When rechecked at the end of the office visit, his blood pressure was 145/90.

An extensive hypertensive workup was done, including hemogram, creatinine clearance, urinalysis, phenosulfonphthalein (PSP), serum glutamic oxaloacetic transaminase (SGOT), urine concentration test, serum electrolytes, calcium and phosphorus, steroids, catecholamines, blood urea nitrogen (BUN), glucose tolerance test, cholesterol, uric acid, and protein-bound iodine (PBI). All were within normal limits, as was the chest film, electrocardiogram, and hypertensive intravenous pyelogram.

In subsequent follow-up visits over the next three months, the patient continued to complain of vague malaise, fatigue, headaches, and nervousness. Blood pressure ranged between 145-190/90-110 in spite of treatment with phenobarbital, tranquilizers, and a modified low salt diet and seemed to be higher at times of stress for the patient. Weight reduction was attempted unsuccessfully because of poor patient cooperation.

Please assume that this patient has "PRIMARY" or ESSENTIAL HYPERTENSION.

Continue to page 2 . . .

Please read the following hypothetical drug description:

DRUG X

(Isomethidinium methosulfate)

INDICATION

Isomethidinium methosulfate, d-[N-isopropyl-N (γ-trimethyl ammonium-propyl)-] 1-ethyl-8, 8-dimethyl-3-azabicyclo [3.2.1] octane dimetho sulfate, is a new, structurally unique hypotensive agent approved for marketing. It occurs as an odorless, white powder soluble in water and in alcohol.

ACTION

The mechanism of action of isomethidinium methosulfate is unknown at this time. The drug does not appear to possess significant ability to inhibit transmission of nerve impulses through autonomic ganglia or at postganglionic sympathetic neuroeffector sites. It also has been shown to have no appreciable effect on the biosynthesis, storage, release, or activity of norepinephrine at the peripheral nerve endings of the sympathetic nervous system. There is little reason to suspect a central activity since the hypotensive response to isomethidinium methosulfate is readily seen in experimental spinal animals.

Extensive studies have demonstrated that, in the treatment of mild, essential hypertension ($<200/<110$), isomethidinium methosulfate has the ability to lower the blood pressure to stable levels. The drug has been demonstrated to produce its peak hypotensive effect within 30 minutes after oral administration (immediate response following i.v. dosage) and has a duration of action of approximately four hours regardless of route of administration. The hypotensive activity is observed only in hypertensive patients and is linearly related to dosage until the ceiling effect for the patient is achieved. The drug has no apparent effect on the vascular dynamics of normotensive individuals.

No tolerance to the therapeutic efficacy of isomethidinium methosulfate has developed over prolonged usage, and the drug can significantly decrease peripheral vascular resistance in hypertensives without inducing orthostatic hypotension, significantly affecting glomerular filtration rate, or inducing hypokalemia.

Isomethidinium methosulfate is totally absorbed from the small intestine, and several spectrophotometric studies have demonstrated that 100% of the drug can be recovered unchanged in the urine. Thus, the drug is not subject to biotransformation prior to renal excretion.

WARNING

In view of the limited time that this drug has been available for general use, it should be used only with extreme caution in combination with other antihypertensive drugs.

DOSAGE

Adults: Isomethidinium methosulfate is usually administered orally to patients. The usual starting dosage is 30 mg. four times daily (with meals and before retiring). The average daily maintenance dosage (oral) is 120-180 mg., with a range of 60-300 mg. The usual intravenous dosage is 15-30 mg. every four hours.

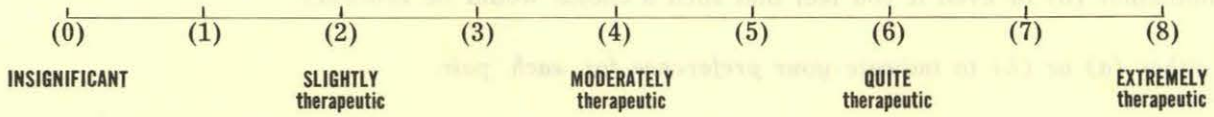
HOW SUPPLIED

White tablets, each containing 30 mg. isomethidinium methosulfate; for intravenous use, 15 mg. of isomethidinium methosulfate/ml., supplied in one ml. ampuls.

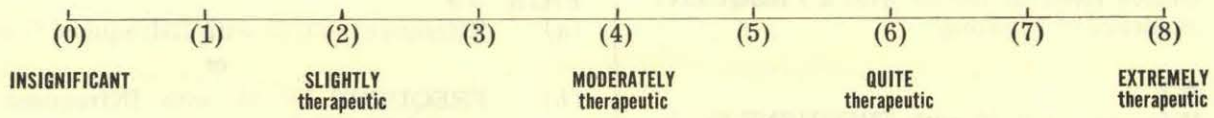
Continue to page 3 . . .

Please answer the following:

If DRUG X produced a stable blood pressure of 150/95 in this patient, how therapeutic would this probably be in terms of both the patient's present state and prognosis? *(make an* X *on one of the nine points):*



If DRUG X produced a stable blood pressure of 120/70 in this patient, how therapeutic would this probably be in terms of both the patient's present state and prognosis? *(make an* X *on one of the nine points):*



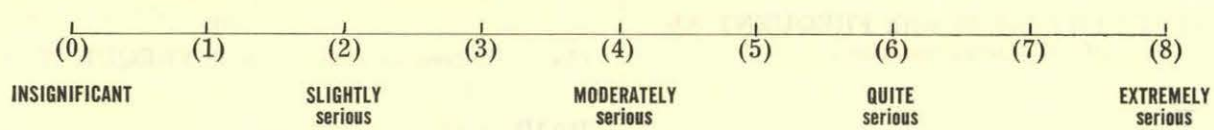
Please read the following:

GLUTAMIC OXALOACETIC TRANSAMINASE: the serum level of this enzyme is increased in diseases involving destruction of liver cells; this enzyme catalyzes the transfer of an amine group from glutamic acid to oxaloacetic acid, forming α-ketoglutaric acid and aspartic acid.

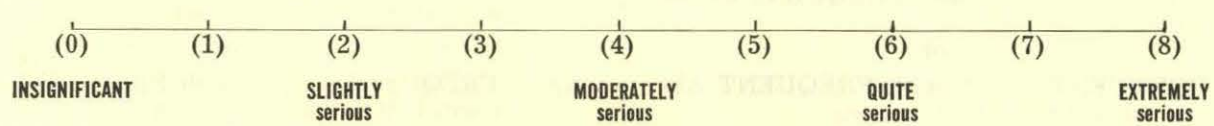
FLUSHING: erythema or redness of the skin.

Please answer the following:

If DRUG X produced ABNORMAL SGOT DETERMINATIONS in this patient, how serious would this probably be in terms of both the patient's present state and prognosis? *(make an* X *on one of the nine points):*



If DRUG X produced FLUSHING in this patient, how serious would this probably be in terms of both the patient's present state and prognosis? *(make an* X *on one of the nine points):*



Continue to page 4 . . .

Each of the following 15 pairs represents two different benefit—side effect combinations producible by DRUG X in mild hypertensives. For each of the 15 pairs, please indicate the benefit—side effect combination you would **PREFER** for the patient described on page 1 by circling either (*a*) or (*b*).

Please make a choice for **each** pair even if you do not particularly like either Combination (*a*) or Combination (*b*) or even if you feel that such a choice would be arbitrary.

Circle either (a) or (b) to indicate your preference for each pair.

PAIR #1

(*a*) FREQUENT incidence of a maximal hypotensive effect of 120/70 with a FREQUENT incidence of Abnormal SGOT Determinations

or

(*b*) FREQUENT incidence of a maximal hypotensive effect of 150/95 with a FREQUENT incidence of Flushing

PAIR #2

(*a*) INfrequent 120/70 with FREQUENT Flushing

or

(*b*) FREQUENT 150/95 with INfrequent Abnormal SGOT Determinations

PAIR #3

(*a*) INfrequent 120/70 with INfrequent Abnormal SGOT Determinations

or

(*b*) INfrequent 150/95 with INfrequent Flushing

PAIR #4

(*a*) FREQUENT 150/95 with FREQUENT Flushing

or

(*b*) INfrequent 120/70 with FREQUENT Flushing

PAIR #5

(*a*) INfrequent 150/95 with INfrequent Flushing

or

(*b*) FREQUENT 120/70 with FREQUENT Abnormal SGOT Determinations

PAIR #6

(*a*) FREQUENT 150/95 with INfrequent Abnormal SGOT Determinations

or

(*b*) INfrequent 120/70 with INfrequent Abnormal SGOT Determinations

PAIR #7

(*a*) INfrequent 120/70 with FREQUENT Flushing

or

(*b*) FREQUENT 120/70 with FREQUENT Abnormal SGOT Determinations

PAIR #8

(*a*) INfrequent 120/70 with INfrequent Abnormal SGOT Determinations

or

(*b*) FREQUENT 150/95 with FREQUENT Flushing

PAIR #9

(*a*) INfrequent 150/95 with INfrequent Flushing

or

(*b*) FREQUENT 150/95 with INfrequent Abnormal SGOT Determinations

PAIR #10

(*a*) FREQUENT 120/70 with FREQUENT Abnormal SGOT Determinations

or

(*b*) INfrequent 120/70 with INfrequent Abnormal SGOT Determinations

PAIR #11

(*a*) INfrequent 120/70 with FREQUENT Flushing

or

(*b*) INfrequent 150/95 with INfrequent Flushing

PAIR #12

(*a*) FREQUENT 150/95 with FREQUENT Flushing

or

(*b*) FREQUENT 150/95 with INfrequent Abnormal SGOT Determinations

PAIR #13

(*a*) INfrequent 120/70 with INfrequent Abnormal SGOT Determinations

or

(*b*) INfrequent 120/70 with FREQUENT Flushing

PAIR #14

(*a*) INfrequent 150/95 with INfrequent Flushing

or

(*b*) FREQUENT 150/95 with FREQUENT Flushing

PAIR #15

(*a*) FREQUENT 150/95 with INfrequent Abnormal SGOT Determinations

or

(*b*) FREQUENT 120/70 with FREQUENT Abnormal SGOT Determinations