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Use of Inderal (Propranolol-Ayerst) in I-a (Early Stimulative) and I-b (Advanced Stimulative) Classification of Cocaine and Other Sympathomimetic Reactions*

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COCAINE PROPRANOLOL

In the I-b ADVANCED Stimulative "CAINE" reaction classically seen in the human at the end of an interrupted 3 to 14 day cocaine per nares or I.V. "run," the progression from the patients' now hyperkinetic behavior, grand mal, clonic, tonic seizures, tachycardia, hypertension, tachypnea, dyspnea, and violent delusional protective behavior, may be autonomically orchestrated by the use of beta blockers, I.V. and P.O. to decrement by astute titration of the patients' vital signs so death does not occur. The concomitant use of antiemetics for control of central nausea and the frequent com-

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plications of hyperthermia and hyperperistalsis may be managed appropriately as indicated by one's clinical skills.

After experiences with over 500 cases of cocaine [13] intoxications we have determined that propranolol has strikingly specific antagonistic effects on the manifestations of central cardiovascular hypermetabolism. After four years of using this drug during "outside rock concerts" we were especially impressed with the specificity of propranolol's action in blocking the cardioaccelerator effects of cocaine.[13]. Dosage was 1 mg/min per I.V. up to a total dosage of thus far 8 mg of propranolol. Hypertension and tachycardia were thus titrated to acceptable clinical levels. Invariably, as well, subjective apprehension, paranoia, and social orientation improved markedly suggesting a central "lytic" effect upon pre-existing sympathomimetic "dopaminergic storm" or crisis. Existing hyperpyrexia and central nausea were not affected [6].

Case Report

During a rock music concert, medical help was sought for a performer who had a history of chronic use of a "large" amount of cocaine, the last dose just having been self injected a few minutes prior to examination, plus a history of having been awake the previous night.

He exhibited the symptoms of chronic adrenergic overstimulation. He spoke in rapid staccato bursts and was initially quite suspicious and difficult to examine. He was pale, nervous, and his extremities were visibly shaking. His pupils were dilated (5 to 6 mm), but weakly light reactive. His mucous membranes were pale and dry. He was intermittently retching and had evidently previously vomited some bile-stained mucoid material. His apical pulse was 140, his peripheral pulse was also about 140 but thready, weak, and difficult to palpate. No rhythm irregularities were noted. His hands were pale, cold, and dry. His blood pressure, also difficult to approximately dertemine, was 220/160 bilaterally by auscultation. Respirations were 40/min and somewhat shallow.

He was observed for 15 min during the usual reassurance "talk down" and patient "space" during which time his vital signs remained essentially unchanged. At this time, propranolol hydrochloride (Inderal) was administered 1 mg intravenously. Within 60 sec his pulse rate was 120, blood pressure was 200/120 bilaterally and respirations were 32/min. Over the ensuing 5 min he was given 1 mg of propranolol at 1 min intervals [13]. Ten minutes following the initial dose, his pulse rate was 88, blood pressure was 140/86, and respirations were 18/min. The peripheral tremors had abated, and his mimetic color was better, although his extremities remained somewhat cold and dry. His pupils remained dilated (4 mm). His mucous membranes remained dry. His

sensorium revealed much less anxiety, and he was given prochlorperazine (Compazine), 10 mg intravenously, whereupon relief of retching was noted after some 3 to 5 min.

At this point, some 30 min after first being seen, he was remarkably free of his initial symptoms and physical signs. His pulse rate was 78, blood pressure was 120/80 bilaterally, respirations were 14/min. Peripheral and central mimetic color were good. He was free of tremor and retching.

After an additional 15 min of rest and monitoring (during which all signs remained stable), he was slowly assisted to the sitting position. Blood pressure rose to 120/90, pulse 74, respirations 12/min. He felt he could "go on now." Within another 15 min he was on stage and playing with his massive electronically amplified group.

He was given a prescription for diazepam (Valium), 10 mg tablets to be taken over the ensuing day on a P.R.N. basis.

The protocol used in this case may be an initial new therapeutic modality for the emergency physician who encounters patients with signs and symptoms of the: 1-b Advanced Stimulation* George Gay Classification of "Caine" Reactions (Table 1) [4].

In another series, over a dozen recreational cocaine users reported a "mellow" (comfortable not hyper) "high" on cocaine after having ingested 40 mg (sometimes more, with unreliable results by history) of propranolol HCl, some 30 to 40 min before nasal and/or I.V. cocaine [13]. This has led to some rather unpleasant side effects, recently, e.g., hyperpyrexia, dyspnea, headache, and diastolic hypertension. Supervention has abolished this practice. The propranolol given simultaneously with clonidine 0.2 mg to 0.4 mg does not increase diastolic hypertension.

The adrenergic receptors "alpha and beta" were so designated by Ahlquist in 1948, and this has helped direct a definition of the myriad pharmacologic responses and interactions of intrinsic and extrinsic drugs of the autonomic nervous system. This allowed categorization and clinical utilization of the various sympathetic alpha and beta agonist and antagonist (or blocking) agents [8].

Koch-Weser has observed "sympathomimetic amines vary only quantitatively in their ability to stimulate alpha receptors, but the inhibitors are highly specific for one or the other." [10]. The authors do not necessarily share the opinion that at least in an emergency situation the inhibitors are indeed "highly specific." Most, if not all, autonomic agonists and antagonists orchestrate, as in music, chords of intricate complexity. It is simplistic but convenient for communication to prefix the word "pure" to any pharmacologic action. Individual autonomic tone and milieu can render a "textbook" agent equivocal or opposite to its expected action (e.g., a "pure" beta-2 antagonist may become a "pure" alpha-1 agonist if the site is "occupied.") Package inserts fail to appreciate such nuances.

*Sometimes called the "walking O.D."

TABLE 1. Gay Classification of 1-b Advanced Stimulation "Caine" Reactions

Phase	Central nervous system	Circulatory system	Respiratory system
1a Early stimulation	Excitement, apprehension, other symptoms of emotional instability, headache, nausea, vomiting. "Twitchings" of voluntary muscles, particularly of face, fingers, arms, thighs.	Pulse varies, probably will slow. Elevation (usual) in blood pressure may occur. Fall in blood pressure may occur. Pallor of skin.	Increased respiratory rate and depth.
1b Advanced stimulation	Hyperkinesis, convulsions (tonic and clonic) resembles grand mal seizure.	Increases in both pulse and blood pressure.	Cyanosis, dyspnea, rapid (gasping), or irregular respiration.
2 Depression	Paralysis of muscles, loss of reflexes, unconsciousness, loss of functions, death.	Circulatory failure, no palpable pulse, death.	Respiratory failure, ashen gray cyanosis, death.

Since 1968, propranolol HCl has been the sole "beta blocker" approved for clinical use in the United States, and as such has become prototypic to our concept of it as a weapon in amphetamine-like overdoses [2]. In truth, this analogue of isoproterenol (and as a corollary) isoproterenol (Isuprel-Winthrop) is the "antidote" for propranolol "O.D.'s"* and has proven pharmacologically to be a "mixed" beta-1 (cardiostimulatory) and beta-2 (bronchodilator and vasodilator) blocking agent, as well as displaying several undefined "nonbeta blocking" properties in varied clinical applications.

Although formally approved by the FDA in the United States for use in the treatment of arrhythmias (1967), angina, (1973), and now hypertension (1976), propranolol continues to emerge as a multifaceted and fascinating chemical adjunct to the observant physiologist/pharmacologist/medical toxicologist. Its caveats are surely recognized (viz., beta-1 suppression of cardiac function, and beta-2 production of bronchospasm); however, newly observed potentials for propranolol's use in clinical medicine surmount the average clinician's illogical fears. We hear the reiterated didactic cants echoing from pharmacologic seers with senses benumbed by potent medicaments and the poor circulation of the back laboratories of academe (or worse, perhaps, of the inertia of political medicine). Some of the "bogey-man" side-effects so propounded must be here decried: the heart still beats in the face of relatively large doses of propranolol; the patient with orthostatic syncope is simply put into a Trendelenberg position; the experienced insulin dependent diabetic patient still knows when he or she is hypoglycemic and will react in kind with P.O. orange juice or I. M. glucagon. If propranolol is contraindicated then give P.O. clonidine 0.2 mg every 15 min. In fact, clonidine may be used to put the chronic cocaine user into "withdrawal," one can make use of this fact in behavior modification techniques.

It has been documented that certain species of Corpinus atramentarius "inky top mushroom" and an African species Coprinus erethistes as well as Clitocybe claviceps from Japan have a compound in them similar to disulfiram; possibly a compound "coprine" recently isolated and synthesized by Hatfield. If ethanol is consumed some hours to days after eating the cooked inky top, then an identical "acetaldehyde storm" occurs indistinguishable from the alcohol-antabuse reaction (tachycardia, "flushing," mydriasis, and dyspnea). These very unpleasant beta-1 and beta-2 adrenergic visitations may be reversed with P.O. propranolol (40 to as much as 240 mg) due to the sometimes 20-fold change in bioavailability in serum levels of propranolol.

Propranolol has elsewhere been freely described as therapeutically efficacious in such varied conditions as in the adjunctive therapy of amphetamine intoxication [2], of thyrotoxic hypercalcemia [9], of thy-

*If uncomplicated and bradycardia becomes a problem; if the patient is alert (and hopefully full of activated charcoal) try I. M. atropine 0.5-1.0 mg to help your patient's dyspnea, mitigating the vagal effect.

roid storm [12], pheochromocytoma [7], "lithium tremor" [11], "action" tremor [23], and migraine [21].

The authors' personal experience and observation include the following therapeutic actions of propranolol:

1. As an antidote for the acetaldehyde intoxication resulting from disulfiram (Antabuse) and ethanol interaction (series greater than 20) [16].
2. As an antidote for the acetaldehyde storm induced by the ingestion of Corprinus atramentarius (cooked inky top mushroom) followed by ethanol [17].
3. As an alleviator of the "flush" discomfiture caused by the ingestion of niacin (nicotinic acid) in therapeutic dosage. Series greater than 12: also a central "calmative" effect [3].
4. In the treatment of tricyclic antidepressant, MAO-inhibitor hyperpressor storms [15].
5. In the treatment of hyperpressor effect of the use of the analeptic doxapram HCl injectable (Dopram). Series greater than 12; utilized as adjunctive therapy in the arousal of young CNS depressant users [6].
6. In the treatment of acute ethanol withdrawal syndrome [19].

In light of our clinical experience, we feel that propranolol further exerts a dose-related (partial) blocking effect on the dopamine receptors of the midbrain (thereby effectively reversing the "dopaminergic crises" as is manifested by dysphoria, etc.), alleviating the CNS disorientation and misinterpretation of consciousness following noncomatose "walking O.D.'s" of LSD; with PCP (phencyclidine) intoxications, concurrently lowering blood pressure, and tachycardia attendant to this same overdosed drug [16].*

Theoretically, we predict a therapeutic usefulness for propranolol in the treatment of "degreaser's (and other solvent) flush" [22], MANEB and ZINEB herbicides, plus caffeine, yohimbine, and ibogaine intoxications (Rappolt, 1976) [16].

Propranolol has long been described as penetrating the blood brain barrier [10]; yet calmative effects have been carefully skirted in definition. But in reviewing the literature, as well as in our own experience, we frequently encounter "relieving anxiety" . . . "makes me sleepy" . . . "like, I'm not excited and wired."

Further, the suggestion of a partial contribution of propranolol's antihypertensive effect through a central mechanism has been speculated by many. Likewise, questions are now proposed as to a direct effect on the kidney in plasma renin activity (PRA) [21].

*P.O. haloperidol (dose is not being reported) prior to "smoking a PCP cigarette" has been reported by some dependable patients to, in essence, abort the stage one PCP experience.

Finally, the demonstrated "quinidine-like" activity of propranolol has yet to be fully explored in therapeutic clinical application [21].

Propranolol is an "impure" beta blocker; it remains, however because of our own recognized "drug-lag," the only agent of this action which is approved (and so available) to our private clinical practice.*

The authors call for further elucidative studies of these fascinating drugs with coats of many colors; specifically, to the demonstrated effects which occur at a midbrain dopamine receptor level [3].

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*Currently a relatively more selective β^1 antagonist, metoprolol tartrate (50 mg tablets-Lopressor-Geigy), is being investigated.

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