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Senior Thesis

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PRISCOLINE, AN ANTIADRENERGIC DRUG

Priscoline* is a brand of benzazoline hydrochloride, the chemical name being 2-benzyl-4, 5-imidazoline hydrochloride. It was formerly known as Priscol Hydrochloride. The drug is a colorless, crystalline, water soluble compound. It's melting point is 171°C, and it is stable under ordinary atmospheric conditions.

Priscoline was first reported to have a pharmacological effect by Hartman and Isler in 1939. They reported a group of imidazoline derivatives of which Priscoline had the greatest depressor effect on blood pressure. Meier and Mueller also reported in 1939 that this new drug also dilates the blood vessels of the skin and mucosa.

Meier and Meyer in 1941 placed the pharmacological action of Priscoline in causing vasodilatation on the sympatheticommetic system and ruled out any cholinergic mechanism. They used an isolated lower extremity of a rabbit, its vascular tone being maintained by epinephrine perfusion. When Priscoline was added to the perfusion a maximum dilatation of the vessels occurred, and the dilatation was maximal regardless of the tone of the vessels maintained by epinephrine quantitatively perfused. When atropine was added to the

* CIBA TRADEMARK
perfusion no changes in the effect of Priscoline were noted, therefore, it could be concluded that Priscoline was an antiadrenergic drug and had no effect on the cholinergic system. Meier and Meyer also observed the increase in skin temperature with the peripheral vasodilatation.

In 1945 Chess and Yonkman verified Meier and Meyers' theory as to the pharmacological action of Priscoline regarding blood pressure and vasodilatation, however they found no adrenolytic effects of Priscoline on the cervical sympathetic functions studied. Salivation was not affected by Priscoline and likewise Pupillary responses. In studying the depressor effect of Priscoline it was found that the blood pressure could be lowered up to 50% of normal for an average of three hours. The effect of the drug is sudden, however the animal's pulse and respiration seemed unaffected throughout the course.

Yonkman in 1946 demonstrated the stimulation of the ileum of dogs by Priscoline. This so-called cholinergic response was blocked by atropine, therefore it would appear that Priscoline here acts on the cholinergic system. This however is not true as the vagus is motor to the intestine and the sympathetic inhibits, therefore by decreasing or obliterating sympathetic inhibition with Priscoline the intestine...
is more active. During this period of Priscoline medication with sympathetic release atropine will decrease intestinal motility to near normal. This may be explained by the action of the vagus, motor or stimulation and this reduced or blocked by the atropine. Therefore, the intestine has been released from both sympathetic and parasympathetic control and Priscoline remains a sympatheticomemetic drug.

In 1946 Ahlquist and Woodbury reported that Priscoline would not reverse the pressor effects of sympatheticomemetic drugs as Ephedrine, but would inhibit their action. This seems to indicate an adrenolytic action of Priscoline probably at the myoneural juncture.

Marzoni, Hendrix and Grimson in 1947 showed that Priscoline depression of blood pressure can be reversed by Pituitrin. Since Pituitrin acts directly on smooth muscle. This finding supports the theory as to the locus of action being the myoneural juncture.

Ahlquist, Huggins and Woodbury in 1947 reported the effects of Priscoline on the heart. An increase in cardiac output was noted which was apparently due to reflex stimulation caused by a decrease in blood pressure. Coronary vasodilatation occurred as a result of the Priscoline acting directly and cardiac stimulation reflexly. It was noted

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that occasionally a rise in blood pressure usually only transient occurred as a result of an imbalance of the peripheral vasodilatation and increased cardiac output.

Reardon, Marzoni and Hendrix have established the following dosage by animal experimentation: 1-3 mg./k. epinephrine reversing effect and 3-6 mg./k. abolishes pressor responses. Nickerson and Goodman have found the effects of Priscoline to persist for 3-8 hours. The drug may be given orally, intramuscularly, or intravenously with equally good results.

The first report as to the clinical investigation of Priscoline was made by Zothe in 1939. A decrease in circulation time to the toe was demonstrated in three healthy individuals and one patient with intermittent claudication. Siedeck in 1941 reported an increase in cardiac output in five healthy individuals and five patients with cardiovascular disease. All subjects noted a feeling of warmth over the body and a reddening of the face and extremities, blood pressure was affected little in the normal subjects and was only slightly decreased if any in the hypertensive patients. DeCennaro and Bertazzi demonstrated in 1941 an increase in gastric motility and hastening of gastric evacuation in all subjects as a result of Priscoline
medication.

In 1942 Rodrigues DeCarvalho demonstrated a reduction of blood sugar level in normal and hyperglycemic individuals by Priscoline. It was administered intravenously and subcutaneously, the latter being more effective. It was also found that the higher the blood sugar level the greater the reduction by the same dosage of Priscoline. The pharmacological action regarding blood sugar is not definite, however it may be the result of increased catabolism of sugar as a result of better peripheral circulation. Frieb during the same year found that Priscoline produced a normal blood sugar in elderly people with hyperglycemia. This finding seems to support the theory of increased peripheral circulation, heat loss and increased cellular metabolism.

In 1948 Green and Ogle compared Priscoline, Etamon and applied heat by well controlled clinical experimentation. They used thermocouples and measured skin temperature changes of the forehead, fingers and toes. It was found that Priscoline was the most effective in raising the skin temperature of both fingers and toes after the subject had been placed in a cold environment inducing vasoconstriction. Priscoline plus body warming could be relied upon to completely abolish vasospasm. These findings make it possible
to differentiate occlusive vascular diseases from vasospastic conditions and to estimate the vasospastic element in all peripheral vascular disease. The method of treatment whether amputation, sympathectomy or by Priscoline or other medication may be more accurately determined as a result of this work.

Priscoline was found to be of diagnostic value in determining gastric acidity by Thiele in 1940. Several hundred patients were tested and it was found that a 10 mg. dose administered subcutaneously resulted in a gastric response rated between caffeine and histamine.

Priscoline has been used clinically as a therapeutic agent quite extensively in Germany and South America with results comparable to those obtained by Grimson and his group at Duke University, School of Medicine. On a number of patients with Raynaud's disease many were completely relieved by Priscoline and all were definitely benefited. Dosage varied from 25 to 75 mg. three times daily, depending on the amount the patient needed for the desired results. Skin temperature and color returned to normal and the patients could tolerate cold during treatment. Several of this group were cured with ganglionectomies and others required Priscoline after ganglionectomy in order to remain
free of symptoms. Patients not having ganglionectomies were well controlled on Priscoline alone.

On a group of fifteen patients in the older age group with arteriosclerotic obstructive disease of the legs, Grimson found that pain decreased and the leg ulcers healed when given 25-50 mg. of Priscoline every 3 to 4 hours. The patients were all tested with Priscoline first and in every case a skin temperature increase on the legs and feet was noted. Five of the patients had gangrenous toes and feet which were amputated and the patients then maintained on Priscoline. Five of the patients were markedly benefited by the test dose, therefore they were treated by ganglionectomy with good results. The remaining five patients were moderately benefited by a maintenance course of Priscoline.

Grimson's group of patients with thromboangiitis obliterans included six, of which five were completely relieved of pain by Priscoline alone or ganglionectomy and Priscoline. One patient did not respond to the test dose of Priscoline, therefore amputation was necessary.

Priscoline was used to treat several patients with causalgia type pain and other circulatory disorders. Results were either complete cure after one or two intramuscular doses or no benefit whatsoever. This group is difficult to evaluate.
because of the non-specific lesion, psychogenic factors and possible hysteria. Priscoline was also used in four patients with venous thrombosis or phlebitis. In each instance the legs became warm, pain decreased and recovery seemed to have been hastened.

Thirty-nine hypertensive patients were treated or tested with Priscoline and reported by Grimson and his group at Duke University, School of Medicine. About 50% of this group responded to the Priscoline test with a significant lowering of blood pressure. Sympathectomies on patients responding to the Priscoline test and not responding to the Priscoline test produced equally good results and several of the patients with persisting hypertension after sympathectomy were controlled satisfactorily on Priscoline. The test dose of Priscoline is 200 mg. given in two 50 mg. intravenous hourly doses and a third 100 mg. dose an hour later. The therapeutic dose varied from 25-75 mg. every 2-4 hours and this dose is insufficient in many cases to produce a decrease in blood pressure even though the test dose resulted in a marked decrease.

These clinical findings support the pharmacological findings as to the effect on blood pressure by Priscoline, a balance or imbalance of cardiac output and peripheral vasodilatation.

Rogers(1) has reported 31 cases of peripheral vascular
disease tested and treated with Priscoline. His results paralleled those of Grimson and his group in every respect. In another group of fifteen patients reported by Rogers(2), age ranging from 46 to 79 years both male and female and all showed evidence of arterial insufficiency to the extremeties, improvement was noted in every case. The duration of symptoms for this group was from five months to five years. Priscoline relieved pain and discomfort of the extremeties to normal or near normal.

Priscoline has been found useful in the relief of pain and therapeutically in acute anterior Poliomyelitis by Smith, Graubard, Goldstein and Bikoff. Seventy-three cases were treated with Priscoline and relief of pain in the extremities in every case was marked or complete. It is not known as yet if there is any definite therapeutic value resulting from this treatment or if it is only symptomatic. Smith, Rosenblatt and Limauro have demonstrated that there is an angiospasm of the extremeties similar to that of Raynaud's disease and this is apparently due to the ganglion envolvement in all forms of acute Poliomyelitis.

Wyatt has treated 50 proliferative and degenerative arthritic patients with Priscoline and found that 88% were definitely benefited. Pain and swelling decreased and an
increase in range of motion was noted. In the moderately severe groups of arthritics only 62% were appreciably benefited and in all cases the treatment had to be continued to maintain the desired results. It is believed by Wyatt that Priscoline does not replace any established method of arthritic therapy but is another aid to be used in conjunction with the accepted methods of treatment. Rogers(1) reports one case of tabes dorsalis in which lightning type headaches were completely relieved by Priscoline. This single case does not mean much, however the theory as to the origin of pain in neurosyphilis and the pharmacological action of Priscoline would lead one to expect such results.

The side effects of Priscoline have been listed by Rogers(1) according to dosage. On dosage ranging from 25-50 mg. three times daily patients have complained of "Goose Flesh" or a crawling sensation in the skin, a feeling of squeamishness in the stomach, flushing of the face and some palpitation. On dosage ranging from 50-75 mg. three times daily about one-third of the patients complained of dizziness in addition to the above. Side effects noted by Grimson and his group in their patients were transient shortness of breath in a few patients, slight increase or decrease in pulse rate, flushing of the face and 20% had temporary dilatation of the pupils. There are
no indications in any report as to any withdrawal symptoms from the drug.

Summary:

Priscoline appears to act at the myoneural juncture of the adrenergic nervous system, its effect being that of blocking adrenalin. The pharmacological effects of Priscoline on the body are: peripheral vasodilatation, flushing and increased skin temperature, increased cardiac output, coronary dilatation, increased gastrointestinal motility with increased gastric secretions and occasional lowering of blood pressure with therapeutic dosage.

Priscoline may be used as a diagnostic test in doses of 200 mg. intravenously (two 50 mg. and one 100 mg. dose an hour apart) and with this test any vasospastic condition will be released. The therapeutic dose of Priscoline ranges from 25-75 mg. every two to eight hours.

Vascular diseases that are benefited by or completely relieved by Priscoline are Raynaud's disease, thromboangiitis obliterans, arteriosclerotic peripheral vascular disease and phlebitis. Diseases such as acute poliomyelitis, proliferative and degenerative arthritides respond to Priscoline by symptomatic relief of pain and discomfort.
Priscoline is contraindicated in cases of peptic ulcer and spastic or ulcerative colitis, chronic or acute. Extreme caution should also be exercised when administering the drug to hypotensive patients or patients with coronary heart disease or cardiac insufficiency. Ephedrine may be used to reverse the vasodilatation in the event of severe vasomotor depression with a markedly lowered blood pressure.
BIBLIOGRAPHY


