CURARE

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Curare, for which urari and woorari are synonyms, first appears in the literature in 1595 in a reference of Hakluyt to Sir Walter Raleigh's voyage up the Orinoco River to Equador. A crude extract of the drug was used by the natives of that territory on their arrows to kill enemies and animals of prey. Sir Walter Raleigh took samples of this crude drug back to England upon his return.[1]

In 1814 Watterton and Brodie suggested that the chief action of this drug was the interruption of the neuromuscular mechanism.[2] Later Claude Bernard undertook the first extensive scientific investigation of the substance, demonstrating that the site of action is at the myoneural junction and that the cause of death is anoxia from paralysis of the diaphragm.[3,4] Since 1857 curare has been used for the treatment of such conditions as tetany, tetanus, strychnine poisoning, and chorea.[5]

The drug was used by Hoffman[6] in 1879 to treat the convulsions in tetanus. The modern purified drug has been produced from samples of curare[7,8] brought from Equador to this country by Gill[9] in 1932. Curare was again employed in tetanus by Cole[10] in 1934, Mitchell[11] in 1935, and West[5] in 1936. Burman[12] treated spastic states with curare in 1939, while in 1940, 1941, and 1942, Bennett,[13] Gray,[14] and Cummins[15] used it to attenuate the convulsions of tetrazol and electric shock therapy in psychiatry.

The first use of curare in anesthesia was reported by Griffith and Johnson[16] in 1942. That year and again in 1943 Cullen[17,18] reported the use of the extract in a large series of anesthesias.

Although crystalline curarine was isolated by Preger[19] in 1864, the curare preparations were somewhat crude and variable until 1943. Three types of the drug are derived from different species of strychnos and are appropriately named for their containers: tubocurare (lengths of bamboo), calabash curare (gourds), and pot curare (clay pots).[19] They yield the alkaloids tubocurarine (and curine), curarine, and protocurarine, respectively. Of these, tubocurarine is the drug in use today and is supplied as an aqueous extract containing 20 units per cubic centimeter. The unit is the equivalent of 1 mg., as determined by the "Head-drop" crossover method.

Chemistry

The active principle of intocostrin* is d-tubocurarine. This substance

* *Intocostrin is manufactured by E. R. Squibb and Sons.*

is a curare alkaloid chemically related to strychnine but of unknown molecular formula.

The action of the alkaloid apparently is not a function of its molecular structure, as a similar action is found in unrelated drugs such as phosphonium, quaternary ammonium salts,[19,20] ethyl ether, pentothal sodium, and tribromethanol.

Mechanism of Action

The alkaloid interferes with the action of acetylcholine on striated muscle so that neither acetylcholine nor a nerve impulse can produce muscle contraction.[21]

Claude Bernard[3] showed in a classic experiment that a nerve bathed in curare can conduct an impulse which excites contraction in an uncurarized muscle.

He showed further that the muscle (frog) in which the blood vessels had been ligated responded to stimulation of the nerve supply, although the animal had previously been curarized.

Curare also has an effect on the sympathetic ganglia, blocking the transmission of nervous impulses between preganglionic and postganglionic fibers.[22] A mild effect which results in relaxation is exerted upon the smooth muscle of the intestine. These facts suggest that curare acts anywhere in the nervous or muscular system where acetylcholine is the chemical mediator.[23] There is some evidence that curare blocks the peripheral response to stimulation of the vagus.

Although the chief action of the drug is demonstrably peripheral, a central depression of respiration has been reported.[24]

Prostigmine is antagonistic to the curare action, as it inhibits choline esterase, a destroyer of acetylcholine.[21] Potassium ions have been shown to exert an anticurare action.[25]

Appearance of Effect

Relaxation follows an intravenous injection of curare in two to four minutes. The first muscles affected are those supplied by the cranial nerves, as evidenced in the un-anesthetized subject by strabismus, diplopia, nystagmus, and weakness of the eyelids, accompanied by relaxation of the muscles of mastication and those of the lower jaw and pharynx, and by impairment of the functions of swallowing and coughing. The muscles of facial expression are relaxed, and speech becomes slow and difficult. The muscles of the trunk and extremities are next involved, and this results in weakness and inability to move the body. The diaphragm is the last skeletal muscle to be affected.

An effective blood level cannot be attained by the oral administration of curare, as it is destroyed and eliminated as fast as it is absorbed.

Furthermore, some of the drug may be changed and rendered ineffective by the process of digestion, as is true of epinephrine and snake venom.

Duration of Effect

The curare effect lasts from twenty to thirty minutes, after which it seems to disappear completely, except that it can be re-established by a smaller amount of the drug than was given in the previous injection.

When properly employed a satisfactory relaxation of the skeletal muscles (excluding the diaphragm) is the usual result. Occasionally the larger dose recommended, or even a dose considered to be moderate, may cause paralysis of the diaphragm and apnea.

Tolerance

No tolerance to repeated doses of curare has been demonstrated in the course of its repeated administration to many hundreds of psychiatric patients during treatment by shock therapy.[21]

Overdose

An overdose of curare is indicated by an irregularity in the respiratory movements and apnea. There is no evidence that any organic damage results from an overdose of curare.

Fate

The alkaloid is partly destroyed by the liver and partly excreted by the kidney.[22]

Side Effects

The side effects of curare when used clinically are few and, for the most part, insignificant.

The electrocardiogram of normal and diseased hearts is not disturbed by therapeutic doses of the drug.[26] Prolonged use may cause a fall in blood pressure as a result of the muscular relaxation and attendant slowing of venous circulation.[27]

The electro-encephalogram shows a suppression of the electrical activity of the frog's brain by administration of d-tubocurarine, a property shared by di-hydrobeta erythroidine, quinine ethochloride, nicotine, and thiamine.

The relaxing effect of curare on the intestines is ordinarily of no significance in the clinical use of the drug.

Technic

Curare can be used effectively with any general anesthetic agent but is not satisfactory when used alone. This is owing in part to the discomfort experienced by a patient so-treated, who is unable to control the vocal cords and the muscles of the throat and jaw which help to maintain an adequate airway.

When used with cyclopropane, an initial dose of 60 units is injected intravenously at the time that the skin incision is made. If this fails to provide sufficient relaxation, one-half to two-thirds of this dose is added in three to five minutes.[22] A similar supplemental injection is made as the effect begins to disappear or when more relaxation is needed. The initial injection varies with different anesthetists but ranges from 60 to 200 units.[1,17,21] The larger initial doses result in apnea for periods up to a half-hour and demand the continued use of artificial respiration, preferably with an intratracheal tube in place. The technic is essentially the same for use with pentothal or nitrous oxide, but when combined with ether the dose must be diminished by two-thirds, owing to the curare-like action of ether itself.

Curare has been used in both extremes of life, for many different types of operations, and in the presence of many complications.

Contraindications

Three contraindications to the use of curare have been cited. Myasthenia gravis, on account of the close resemblance of its symptoms to the curare effect, forbids administration of the drug. Its use is inadvisable when the anesthetist is unable to perform artificial respiration on account of such factors as the position of the patient and respiratory obstruction. Impaired renal function which may retard the elimination of the drug has been cited as a contraindication,[19,21] but other anesthetists do not consider this a serious objection.

Complications—Postanesthetic

There has been no reported organic damage which results from the use of curare. Untreated apnea, however, may lead to hypoxea.

At Cleveland Clinic curare is used as a supplement to the general anesthesia induced by ether, tribromethanol, nitrous oxide with oxygen, and pentothal. It is most frequently employed to improve exposure and facilitate closure during abdominal operations, thus supplementing a spinal anesthetic combined with pentothal.

It is serving to supplement an increasing number of pentothal anesthesias given for laryngoscopy, laryngeal intubation, bronchoscopy,

and esophagoscopy. In this type of procedure the curare (usually 60 units) is given as soon as the venipuncture is made, the needle then being flushed by the withdrawal and reinjection of 1 or 2 cc. of blood before attaching the pentothal syringe or tubing. This precaution is taken in order to avoid injecting the precipitate which results from mixing pentothal and the curare extract in the concentrations generally employed. The pentothal anesthesia is then begun immediately, the patient going to sleep before the discomfort of the curare effect appears.

The relaxation afforded by the curare greatly improves the exposure of the larynx (previously cocainized) for biopsy or intubation and is of especial value in short, thick-necked, heavy smokers who have a hyperactive pharyngeal reflex.

In some patients spinal or caudal anesthesia is contraindicated because of an inflamed condition of the skin in the area of the injection. When these patients require treatment for anorectal diseases, pentothal and curare provide satisfactory relaxation.

Conclusions

Curare extract (intocostrin) contains an alkaloid of unknown molecular formula which blocks the neuromuscular passage of impulses. This effect is much more pronounced in skeletal muscle, and it is this quality which renders the agent useful to the anesthetist. The only significant danger from its use is paralysis of the diaphragm, which results from the use of larger doses. The resulting apnea can be readily controlled by artificial respiration.

The development of curare represents a significant advance in anesthesiology.

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ACUTE LEFT VENTRICULAR FAILURE

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Acute left ventricular failure, characterized by an agonizing struggle for air, is terrifying to the patient, family, and physician. The seizure is distinctive, therefore most contemporary descriptions are similar. Probably the first account of this syndrome was that of Aretaeus of Cappadocia.[1] His words paint a picture that has been little improved upon in the 2000 years since his death. In patients with paroxysmal nocturnal dyspnea, "the cheeks are ruddy; eyes protuberant, as if from strangulation; . . . voice liquid and without resonance; a desire of much and of cold air; they breathe standing, as if desiring to draw in all the air which they possibly can inhale; and, in their want of air, they also open the mouth as if thus to enjoy the more of it; pale in the countenance, except for the cheeks, which are ruddy; sweat about the forhead and clavicles; cough incessant and laborious; expectoration small, thin, and cold, resembling the efflorescence of foam; neck swells with the inflation