Beinvloeding van experimenteel boezemfibrilleeren door therapeutische of toxische doses van verschillende medicamenten?

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Summary

My investigations were carried out with the object of determining the antifibrillatory action of several medicaments, and also whether the antifibrillatory action was present before or after the appearance of the first toxic symptoms.

A commencement was made with the following Barbituric acid preparations: Veronal-Sodium, Dial, Pernocton, Somnifen and Evipan-Sodium.

Van Dongen was unable to find any influence whatever on fibrillation after the use of these substances.

In the five experiments which I carried out with Veronal-Sodium the values for post-fibrillation came to zero in three cases, after a gradual fall had first made itself evident.

In two of these three cases the values for fibrillation also came to zero, so that a complete therapeutic effect would have been attained if no dilatation of the ventricles had occurred before that time. A toxic injury to the heart had therefore taken place. The therapeutic dose was therefore larger than the maximum dose.

I therefore found, in contrast with Van Dongen's results, an antifibrillatory effect, although the drug, as a specifically antifibrillatory drug, was found to be too toxic.

Pernocton showed a decline to zero of the values for post-fibrillation in only one of the five tests.

In every case the decline was very rapid, and accompanied by an equally rapid intoxication of the heart. This drug cannot be said to have any antifibrillatory properties.
With Somnifen a fall to zero was attained in four of the five post-fibrillation cases, both for fibrillation and post-fibrillation.

In the fifth experiment only the value for fibrillation of the right auricle remained above zero.

There was therefore an antifibrillary action in this case also, but as the therapeutic effect first made its appearance after dilatation of the ventricles, the therapeutic dose was higher than the maximum dose and the drug therefore too toxic.

Dial showed a fall of the values for post-fibrillation to zero in three of the five cases, but only after the cardiac action had become bad a considerable time before. The drug is pretty toxic for the heart and so has no specifically anti-fibrillating properties.

The last of the Barbituric acid preparations which I investigated for antifibrillating properties was Evipan Sodium. This drug showed in one case a fall of the values for post-fibrillation to zero. In the other cases a slight fall occurred only for post-fibrillation, whilst the values for fibrillation remained practically constant. Moreover only at most five injections were required to reach the lethal dose. The anti-fibrillatory action is therefore in this case purely a result of the intoxication of the heart.

The Barbituric acid preparations which I investigated therefore possess antifibrillatory properties, but are on the other hand too toxic to be used as a therapeutic drug, as in every case the therapeutic dose is above the maximum dose.

Van Dongen found an anti-fibrillatory action after the use of Luminal, and attributed this probably to the influence of the phenyl group which Luminal contains. He therefore investigated Antipyrine and Pyramidon, which also contain a phenyl group.

He was, however, disconcerted by the latter substances. In the five fibrillation cases the values for fibrillation came in for fibrillation, but only after dilatation of the ventricles. The same was also the case in this case as the therapeutic and post-fibrillation values for fibrillation and post-fibrillation both occurred simultaneously. The therapeutic dose was above the maximum dose. The therapeutic action was therefore close together, and therefore possessed a combination of substances.

After Chowlala's investigation of Luminal, the fibrillation values had a fall of the fibrillation values for fibrillation, albeit at the same time. This therefore accounted for the Antipyrine and Pyramidon being above the six cases. The therapeutic action, however, also for the Antipyrine and Pyramidon.

As, however, the fibrillation values for fibrillation have fallen below the fibrillation value before fibrillation, it is therefore possible to use as a comparison with the fibrillation.
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raine and phenyl group.

He was, however, unable to trace any effect of these latter substances on fibrillation.

In the five experiments which I carried out with Antipyridin, the values for fibrillation and post-fibrillation came in four cases to zero, after the occurrence of a slow and regular fall of all the values, so that an antifibrillatory property is undoubtedly present.

The same picture was shown by Pyramidon. In this case all the values fell to zero, both for fibrillation and post-fibrillation. Dilation of the heart occurred simultaneously with the fall to zero or a short time before it.

The therapeutical dose and the maximum dose are close together in these two drugs; although they therefore possess a distinct antifibrillatory power, both substances are just a little too toxic. After Chloralhydrate the values came in three of the five cases to zero both for fibrillation and post-fibrillation. This fall followed suddenly after the values had remained practically constant, whilst at the same time dilatation of the ventricles occurred. This is therefore a typical toxic fall of the values.

Cardiazol showed a fall of the values for post-fibrillation to zero in three out of the six experiments, before dilatation of the ventricles occurred. In two of the six cases the values of fibrillation also fell to zero; this, however, after the ventricles were already dilated. Cardiazol therefore has anti-fibrillatory properties.

As, however, with a good antifibrillation drug the values for post-fibrillation and also for fibrillation must have fallen to zero before symptoms of cardiac intoxication occur. Cardiazol is also still too toxic for use as a complete therapeutic.

Coramine yielded a fall of the values for fibrillation and post-fibrillation to zero in two of the five
experiments. In these cases, however, dilatation of the ventricles had already previously occurred and the cardiac action was also pretty bad. In this case, too, the antifibrillatory action is a result of the cardiac intoxication.

Digitalis showed a fall of the values for fibrillation and post-fibrillation in two of the cases, the lethal dose also being reached. Here again, therefore, we have a toxic fall of the values, and not a specifically antifibrillatory effect.

Finally it follows from six experiments with Strophanthin that this drug possesses no anti-fibrillatory properties whatever. After use of this drug death occurred after the values both for fibrillation and for post-fibrillation in most cases had not fallen at all.

Conclusion

The substances of the Barbituric acid group investigated by me possess anti-fibrillatory properties. As therapeutic drugs they are of no use, as the therapeutic dose is larger than the maximum dose. The same holds good of Antipyrin, Pyramidon, and Coramine.

In the case of Digitalis and Chloral hydrate the therapeutic dose and the lethal dose coincide.

After a therapeutic dose of Cardiazol no post-fibrillation can be brought about, whilst this is possible for fibrillation only after a maximum dose has been exceeded.

Strophanthin and Antipyrin in a lethal dose cause death from ventricle fibrillation.

The fact that in all my experiments, in which Strophanthin was used, death occurred from ventricular fibrillation, for caution thin injections administered not under the cases have conditions also intravenous. The states administration after my in A substance fibrillatory are smaller which toxic difference fibrillatory. Many subst when the
fibrillation, I consider to be of importance clinically. For caution is necessary with intravenous strophanthin injections not only when digitalis has been administered shortly before, but also when the patient is not under the influence of digitalis. Cases have been observed in which, under those conditions also, death has occurred immediately after the intravenous injection. The states of collapse which may occur after oral administration of antipyrine are also seen in a new light after my investigation.

A substance may therefore be effective as an anti-fibrillatory drug in therapeutic doses, if these doses are smaller than the maximum dose, i.e. the dose at which toxic effect is brought about. The greater the difference between the two is, the better the anti-fibrillatory properties are.

Many substances possess anti-fibrillating properties when the maximum dose is exceeded, that is, only when the dose is toxic.