SPECIAL LECTURE**Evaluation of anabolic steroids.****G. A. OVERBEEK**

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Research preceding clinical use of drugs aims at the best possible prediction of the effects in man.

The chemist envisaging new structures has only very few leads that will enable him to prepare a drug with the desired properties. If the drug should be an anabolic steroid these properties should be high anabolic activity, absence of androgenicity and other side effects. In order to achieve this he will prepare derivatives either of androstan-17 β -ol or 19-nor-androstan-17 β -ol. If he wants an orally active substance he will introduce a 17 α -methyl- or ethyl group. If he wants a long acting parenteral drug he will esterify the 17 β -hydroxy group.

Other changes that have been or are likely to be successfully applied, such as double bonds or substitutions at the carbon atoms 1, 2, 4, 6, 7, 9, 11, 16 or 18 mainly haphazard.

The animal pharmacologist is in a better position. A wealth of data obtained by the study of many compounds with only a few methods are available and at least a number of the compounds have also been applied in man. This would make it fairly easy to judge the value of the methods, were it not that the final results obtained with one and the same approach e.g. the levator ani method may differ greatly depending on choice of criterion, rate and frequency of administration, and mathematical use of the figures.

The measurement of nitrogen retention gives quite different values for anabolic activity from that based on the myotrophic effect as determined by the levator ani method, and the activities found in different animal species (rat, monkey) also differ greatly.

Great differences are also found when evaluating the androgenic activity by means of growth either of seminal vesicles or ventral prostate. The use of a standard preparation does not eliminate these difficulties since different steroids affect both organs in a different, unrelated and hence unpredictable manner. Some particularly striking examples of such differences both with respect to anabolic and androgenic activity will be presented.

The assay method to be selected must meet the following two requirements:

1. There should be the best possible agreement between animal and human data.
2. The highest possible accuracy should be obtained.

In order to achieve this, dogmatic starting points must be avoided. Perhaps unexpectedly one finds that for these studies the monkey is not preferable to the rat and

the measurement of nitrogen retention is not preferable to that of the levator ani weight as a criterion for anabolic activity.

There are two points where dogmatism is desirable namely with respect to route and frequency of administration. Oral preparations have to be administered by the oral route and parenteral longacting preparations should be injected once weekly or biweekly and not daily as is often done. The influence of different patterns of administration will be demonstrated by the results of experiments with nandrolone, nandrolone phenylproprinate (Durabolin) and nandrolone decanoate (Deca Durabolin).

A different problem concerns the choice of the mathematical processing of the data, if possible leading to one or two figures that make it easy for the clinician to select the preparation most suitable for the particular patient. Preferable is the use of potency ratio's ($R_{anab.}$ and $R_{andr.}$) expressing the anabolic and androgenic activity in terms of the activity of a standard preparation. From these potency ratio's an anabolic/androgenic ratio $Q = \frac{R_{anab.}}{R_{andr.}}$ can be calculated. (It should be remarked that other investigators use the term anabolic/androgenic ratio and the same letter Q in a quite different way which makes these terms not comparable to those mentioned above.)

These R and Q values are calculated from the dose response curves. They are independent of the dose in the dose range where these curves are parallel. Other calculations making use of only one particular point of the curve, such as the threshold dose or the dose required for substitution to normal, involve the fact that when the dose response curves are not parallel the results apply only to the dose level studied, of which no one can judge the equivalent in the human.

Although strict parallelism of dose response curves of structurally different compounds probably does not exist, the curves were in a number of cases found not to deviate statistically significantly from parallelism. This will be demonstrated to be the case for the oral anabolics methyltestosterone (standard), norethandrolone (Nilevar), ethylestrenol (Orgabolin), and methandrosthenolone (Dianabol). The R and Q values obtained will be presented.

The human pharmacologist is able to obtain an impression of the anabolic activity of steroids by studying their effects on the nitrogen balance in normal subjects. Because of the labour and time involved he will rarely be able to make dose response curves and he will usually compare the substances by determining their respective threshold doses. It is fortunate that these threshold doses for shifting the N-balance in a positive direction are certainly not lower than the average clinical dose, since for the latter purpose threshold doses are obviously uninteresting. Studies performed by van Waijen with androstanazol (Stromba), ethylestrenol (Orgabolin) and oxymetholone (Adroyd) show that these effects on the human correspond better with the results of the levator ani assay than with the nitrogen retention test in the rat.

The evaluation of androgenic activity in the human, especially in women and

children these being the most important subjects with respect to clinical side effects, is impossible for technical and ethical reasons.

The clinical evaluation yields hardly more than impressions of the magnitude of anabolic and other properties. Figures of some interest in this respect are the daily doses advised by the pharmaceutical houses. As will be shown for six much used preparations those doses indicate that the clinical activity agrees better with the results of the levator ani assay than with those of the nitrogen retention test in the rat.

Conclusion

When the levator ani test is used correctly and the data obtained are computed as indicated, the results are in satisfactory agreement with experience in humans.