Time-Response Curves in the Evaluation of the Clinical Efficacy of Drugs

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Received: March 9, 1971, accepted: June 7, 1971

Summary. Statistical models based on negative binomial and Erlang's distributions have been used to describe the temporal development of the therapeutic effects observed during a clinical study of triacetyl-6-azauridine in psoriasis. The usefulness of such models for the prediction of the time of first appearance of therapeutic or unwanted side-effects during repeated drug administration is discussed.

Key-words: Clinical evaluation, psoriasis, statistical models, time-response curves, triacetyl-6-azauridine.

Time is an important factor in the therapeutic effectiveness of repeated drug administration because many drug effects appear only after a definite lag period which varies from patient to patient. Unfortunately, only relatively small numbers of patients can be used in the early stages of clinical experimentation thus giving only limited information about the therapeutic effects to be expected in a large scale clinical trial. This information may be even more important if undesirable side-effects appear during treatment even though they may be rare. The establishment of well-defined time-response curves should therefore represent an integral part of the clinical assessment of new drugs.

In our laboratory statistical models based on negative binomial and Erlang's distributions have been used to describe the temporal development of chronic toxicity of drugs in animal experiments. The basic assumption which both these models have in common is that "chronic effects" of drugs appear as a result of accumulation of a "critical number of primary effects", occurring at random and not manifesting themselves by an obvious reaction of the organism (Janků, 1960; Janků and Šampalk, 1970). In a similar manner, therapeutic effects obtained by repeated drug treatment in humans may also be regarded as "chronic effects", and as due to accumulation of "primary effects" which the drug exerts at a lower level -- cellular or subcellular -- of action. Therefore, we have tried to utilize these models for the establishment of time-response curves for the therapeutic effects of triacetyl-6-azauridine -- a cancerostatic drug which has recently been used successfully for the treatment of psoriasis and mycosis fungoides (Záruba, Kůta and Elis, 1963; Calabresi, Turner and Lefkowitz, 1964; Calabresi and Turner, 1966; Slavík, Elis et al., 1970).

Material and Methods

1. Clinical evaluation. The raw data analysed in the present paper were taken from a more detailed study of the therapeutic effectiveness of triacetyl-6-azauridine in psoriasis (Slavík, Elis et al., 1970). Nine patients suffering from psoriasis were given a daily oral dose of 150 mg/kg of triacetyl-6-azauridine for a period ranging up to 12 weeks. The following three parameters were regularly assessed in each patient as indicators of the severity of the disease:
   a) the extent of skin affected
   b) the height of skin efflorescence
   c) the degree of skin desquamation

The first parameter was expressed as a percentage of the whole body surface and was evaluated using the tables of Lund-Browder for the measurement of skin burns. The second and third parameters were estimated in three degrees: 1. moderate 2. medium and 3. strong.

The therapeutic effect of triacetyl-6-azauridine was judged according the following two criteria:

A. The criterion of "first improvement" was achieved when inhibition of further development of the disease occurred in all of the three parameters considered.

B. The minimal area of affected skin found during the entire period of treatment and accompanied by a reduction in the other two parameters was designated as "best effect".

2. Statistical evaluation. For the establishment of the time-response curves based on the negative binomial distribution, the mean number of daily (weekly) doses \( \bar{x} \) necessary to produce the therapeutic effect specified by the criterion and the corresponding variance \( s^2_x \) were first calculated. These values were then used for estimation of the parameters of the negative binomial model: the critical number of daily (weekly) doses \( r \) representing the minimal number of daily (weekly) doses necessary to produce the specified effect, as well as the probability \( p \) that a primary effect is produced by a daily (weekly) dose according to the following formulae:

\[
\begin{align*}
    r &= \frac{s^2_x}{\frac{s^2_x}{\bar{x}} + \bar{x}} \\
    p &= \frac{\bar{x}}{\frac{s^2_x}{\bar{x}} + \bar{x}}
\end{align*}
\]
If Erlang’s distribution was assumed to represent the model of the cumulative time-response curve, the mean lag period $t$ and the corresponding variance $s_t^2$ were calculated first. The estimation of the model parameters, e.g. of the “critical number of primary effects” $q$, as well as of the “intensity of the therapeutic process” $\lambda$ representing the mean increment of “primary effects” per unit of the time scale selected, then proceeded according to the formulae:

$$ q = \frac{\bar{t}^2}{s_t^2} \quad \lambda = \frac{\bar{t}}{s_t^2} $$

The theoretical time-response curves which were compared with the observed cumulative frequencies were constructed as follows:

$$ F(x) = \sum_{i=r}^{\infty} \left( \frac{i-1}{r-1} \right) p^r (1-p)^{i-r} \quad F(x) = 0 \text{ for } i < r $$

in case of the negative binomial model, and

$$ F(t) = 1 - \sum_{n=0}^{\infty} \frac{(\lambda t)^n}{n!} e^{-\lambda t} $$

in the case of models based on Erlang’s distribution.

**Results**

The original results of chronic treatment of the group of nine psoriatic patients with a daily oral dose of triacetyl-6-azauridine 150 mg/kg using the two selected criteria of therapeutic effectiveness are shown in Table 1.

**Table 1. The results of daily oral treatment of psoriatic patients with 150 mg/kg of triacetyl-6-azauridine**

<table>
<thead>
<tr>
<th>Patient</th>
<th>“First improvement”</th>
<th>“Best effect”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>days</td>
<td>weeks</td>
</tr>
<tr>
<td>1. S.J.</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>2. F.S.</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3. V.V.</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4. V.K.</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>5. P.J.</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>6. S.A.</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>7. A.M.</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>8. P.J.</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>9. K.M.</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Mean</td>
<td>5.8</td>
<td>7.9</td>
</tr>
</tbody>
</table>

*a Taken partly from Slavík, Elis et al. 1970.*

The model parameters calculated from these data are summarized in Table 2. It is interesting to observe that the “critical number of primary effects” representing one of the model parameters based on Erlang’s distribution is the same regardless of the criterion which was used for the evaluation of the therapeutic effect. The difference is only in the second parameter of this model — the “intensity of the therapeutic process” — which, of course, is much lower for the achievement of the “best effect” than for mere “first improvement”. On the other hand, the observed numerical identity of the “critical number of doses” used as parameter of the negative binomial model is only apparent, since for “first improvement” we have...