THE CLINICAL DOSE RESPONSE TO ASPIRIN

BY

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SUMMARY

Graded doses of aspirin and a placebo were given to a total of 500 patients, in three hospitals, in an attempt to define the degree of precision and repeatability with which a dose-response relationship could be established. Evaluation of pain and relief was subjective, side effects were noted, and several approaches to statistical analysis of results were used. The investigation was divided into five separate studies; although a dose-response relationship emerged in each study there was considerable variation and the implications of this are discussed.

These studies followed those previously reported with aspirin and nepenthe (Parkhouse, Collie and Wood, 1967) and with aspirin and paracetamol (Parkhouse and Hallinon, 1967). They represented an attempt to define more clearly the repeatability and sensitivity of the technique of subjective clinical evaluation of mild analgesics. The purpose was to find out whether a dose-response relationship to aspirin could consistently be established on a single-dose basis in patients with postoperative pain.

METHOD

Wholetime trained nurse-investigators saw patients at hourly intervals and assessed pain and relief. The general technique of the investigation was as previously described (Parkhouse, Collie and Wood, 1967; Parkhouse and Hallinon, 1967) using standardized data cards from which computer analysis of results could be undertaken (Parkhouse, 1967a). The patients were all suffering from postoperative pain of a type for which aspirin or a similar drug would normally have been given. Each patient was studied for one dose only, routine analgesic therapy being prescribed thereafter. It was understood throughout the investigation that any patient could be given a further analgesic at any time if satisfactory relief had not been obtained from the test medication, his subsequent pain and relief scores being discarded. All test medications were made up in the form of identical tablets and were given in a predetermined random order; the investigation was double blind throughout and the nurse-investigators did not know what drugs or what number of different medications were included.

The investigation comprised five studies; each study included 100 patients. In each of the five studies there were the same four medication groups: placebo, aspirin 300 mg, aspirin 600 mg, aspirin 1,200 mg. Thus, in each study approximately 25 patients received each medication. The medications were given in a fixed dose, regardless of age, sex or body weight.

Three hospitals participated in the investigation, two general hospitals and an orthopaedic hospital. Two of these were the same hospitals which contributed cases to the previously reported study of aspirin and nepenthe (Parkhouse, Collie and Wood, 1967). In the present investigation three of the five studies were carried out in the orthopaedic hospital and one general hospital (Studies 1419A, 1419B and 1425A). The same nurse-investigator (M.R.-L.) remained throughout these three studies and thus saw 300 patients consecutively (over a period of approximately 12 months); the great majority of the patients were, in fact, orthopaedic patients. In the second general hospital a second nurse-investigator (M.S.) carried out one study (Study 1422A) and a third nurse-investigator (H.P.) carried out the remaining study (Study 1422B) so that these two nurse-investigators saw 100 patients each. Studies 1422A and 1422B were carried out during the same period of time as the three studies based on the orthopaedic hospital.

Each nurse-investigator worked quite independently; M.R.-L. spent a practice period with
a previous nurse-investigator (P.H.) before begin-
ning work; M.S. spent a practice period with
M.R.-L. and H.P. spent practice periods with
both M.S. and M.R.-L.

RESULTS

Figures 1–5 show the mean scores for total pain
relief, with standard errors, for the individual
medication groups in each of the five studies. Both

patients' opinions and investigators' assessments
are shown. The cumulative results from the ortho-
paedic hospital are illustrated in figures 6 and 7;
figure 6 shows the mean scores and standard
errors for the first 200 patients (Studies 1419A
and 1419B combined) and figure 7 shows the
same information for all 300 patients seen by
M.R.-L. (Studies 1419A, 1419B and 1425A
combined).

![Fig. 1](https://example.com/fig1.png)

![Fig. 2](https://example.com/fig2.png)

![Fig. 3](https://example.com/fig3.png)

![Fig. 4](https://example.com/fig4.png)

Mean total pain relief scores (ordinate) derived from patients' opinions (solid line) and investi-
gators' assessments (dashed line), with standard errors for four medications. Doses (abscissa)
are milligrams of aspirin. Numbers in brackets are numbers of patients contributing to mean
and standard error.
Mean total pain relief scores (ordinate) derived from patients' opinions (solid line) and investigators' assessments (dashed line) with standard errors for four medications. Doses (abscissa) are milligrams of aspirin. Numbers in brackets are numbers of patients contributing to mean and standard error.

**FIGS. 5, 6, 7**

**TABLE I**

*t*-test comparisons with approximate values of *P* between pairs of medications for five individual studies and some combined studies (see text). Patients' opinions and investigators' assessments make up first and second row of each comparison.

<table>
<thead>
<tr>
<th>Dose comparison (mg)</th>
<th>1419A</th>
<th>1419B</th>
<th>1419</th>
<th>1425A</th>
<th>1425A+</th>
<th>1422A</th>
<th>1422B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–300</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>0–600</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>0–1200</td>
<td>&lt;0.01</td>
<td>&lt;0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>300–600</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>300–1200</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
<td>n.s.</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>600–1200</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Table I shows a statistical analysis of the comparisons between medications, in all five studies, on the basis of multiple \( t \) tests. A more desirable form of analysis, based on Duncan's (1955) multiple range test (Snedecor, 1956) and using Kramer's (1956) extension for unequal numbers of replications, is given in Table II, indicating where differences occurred on the basis of an overall significance level of 5 per cent. The "between medications" difference derived from the analysis of variance in each study (F value) is also shown.

**Table II**

**Multiple range comparison between medications based on investigators' assessments.**

The overall level of statistical significance is 5 per cent, and medications joined by a continuous line do not show a significant difference at this level (e.g. in Study 1425A, there was no significant difference between placebo and aspirin 300 mg, between aspirin 300 mg and aspirin 600 mg, between aspirin 600 mg and aspirin 1200 mg). There was a statistically significant difference between placebo and aspirin 600 mg, and between aspirin 300 mg and aspirin 1200 mg). The F value derived from the analysis of variance in each study is shown in the second column.

<table>
<thead>
<tr>
<th>Study</th>
<th>F (between drugs)</th>
<th>Dose (mg)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>No. pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1419A</td>
<td>&lt;0.05</td>
<td>300 1200 600</td>
<td>96 76 64 60 56 25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1419B</td>
<td>&lt;0.05</td>
<td>300 600 1200</td>
<td>40 36 32 24 20 25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1425A</td>
<td>&lt;0.01</td>
<td>300 600 1200</td>
<td>58 23 23 15 15 26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1422A</td>
<td>&lt;0.01</td>
<td>300 600 1200</td>
<td>91 83 52 40 22 23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1422B</td>
<td>&lt;0.01</td>
<td>300 600 1200</td>
<td>93 93 89 67 57 27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table III shows the percentage of patients in each medication group, for each study, who had not received a subsequent analgesic at the stated time after test medication. The number of patients in each medication group who were assessed 1 hour after medication was taken as 100 per cent. For discussion see text.

**Table III**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg)</th>
<th>Hour</th>
<th>No. pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1419A</td>
<td>300</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>1419B</td>
<td>300</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>1425A</td>
<td>300</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>1422A</td>
<td>300</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>1422B</td>
<td>300</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

These regressions are based on the total relief score for the whole period up to 6 hours as assessed by the investigator.

Table IV shows the results of multiple regression analysis carried out on the 300 cases derived principally from the orthopaedic hospital. This analysis was undertaken in order to assess the effect of age, sex and body weight on the response to a given medication. Since all the data in these three studies (1419A, 1419B and 1425A) were obtained by the same nurse-investigator they were pooled for this purpose, thus yielding four medication groups each comprising approximately 75 patients.

**DISCUSSION**

In each of the five individual studies, analysis of variance showed a statistically significant difference between medications. Nevertheless, the variations in the pattern of dose-response which may
Log-dose response regression showing points for mean total relief scores (investigator's assessment) and regression line for three doses of aspirin (0 = 300 mg, 1 = 600 mg, 2 = 1200 mg). The F value for the slope of the line and its statistical significance are indicated with the Study number to which the figure refers.
be observed in a clinical study of aspirin are evident from figures 1–5. Two of the studies (1419A and 1422A) support the commonly held belief that the optimum dose of aspirin is 10 grains (600 mg) and that larger doses do not produce greater pain relief. The other three studies suggest the opposite conclusion.

In general terms, the results obtained principally from the orthopaedic hospital were more successful than those obtained entirely from a general hospital (Studies 1422A and 1422B). This overall difference, however, represents a complex interplay of variable factors which it is not easy to separate out. Firstly, the investigator who worked essentially in the orthopaedic hospital (M.R.-L.) remained throughout three studies and thus became more experienced than either of the other two investigators. In terms of log dose/response regression, her results improved steadily throughout her three studies, thus suggesting that experience is a factor to be taken into account. The same may be said to be true with regard to this investigator’s tendency to discontinue scoring and administer a subsequent medication in the case of those patients who had not obtained appreciable relief (table III). But considering the circumstances of the investigation, and considering that Study 1419A was undertaken after only a brief practice period, the evidence of improvement with experience is perhaps slighter than would be expected.

Secondly, it may be argued that an orthopaedic hospital is an inherently better place for this kind of investigation than a general hospital (Parkhouse, 1967b). Most patients undergoing orthopaedic surgery are healthy and psychologically well adjusted; the postoperative course is uncomplicated in comparison to that of many forms of general surgery; pain is of a type which often responds well to aspirin and the assessment of this relief tends to be clear cut. The fact that neither of two investigators who worked exclusively in a busy general hospital was able to obtain as good a dose-response as the investigator who worked mainly at an orthopaedic hospital lends support to this contention.

Thirdly, there remains the rather obvious possibility that investigators may vary in their ability to discriminate between drugs and in their general aptitude for this kind of work.

It is unusual for a clinical trial to be repeated in the present manner. Hence the relative importance of these factors, the experience of the investigator, the difference between hospitals and the influence of the investigator’s personality, have received little attention. Although the present investigation may be said to shed some light on these intriguing questions, no conclusive pronouncement can be made and a truly searching analysis remains to be carried out.

The $t$ test was not designed for the multiple comparison of many pairs of treatments in a trial designed along the present lines (Parkhouse, 1967c). The multiple range test is an attempt to overcome this objection, by establishing an overall level of statistical significance for all differences found. It is interesting to note, particularly for those who are anxious to uphold the “robustness” of the $t$ test, that in the present investigation a total of thirty comparisons between pairs of medications was made; as judged by the $t$ test and the multiple range test the occurrence of significant and non-significant differences (at the 5 per cent level or greater) was identical, except that in Study 1419A the multiple range test indicated no significant difference between placebo and aspirin 300 mg, while the $t$ test indicated a difference at the 0.05 level in the case of the investigator’s opinion (no significant difference in the case of the patient’s opinion). For the difference between

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### Table IV

Regression of investigators’ assessment on stated factors in three combined studies carried out principally at an orthopaedic hospital (Studies 1419A, 1419B and 1425A). For discussion see text.

<table>
<thead>
<tr>
<th>Aspirin (mg)</th>
<th>Patient’s assessment</th>
<th>Age</th>
<th>Age¹</th>
<th>Sex</th>
<th>Age²</th>
<th>Weight</th>
<th>Weight²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.001</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>300</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>n.s.</td>
<td>n.s.</td>
<td>&lt;0.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>600</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>1200</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

¹: Age adjusted
²: Sex adjusted

placebo and 600 mg aspirin in Study 1422B both tests gave a borderline result.

As an alternative to the computation of statistically significant differences, a crude assessment of the efficacy of drugs may be obtained by noting the time interval after which a further drug is required. This is the basis of table III, which shows the percentage of patients who “survived” for various periods of time without requiring a subsequent analgesic after the various medications, in the five individual studies. Although in Study 1419A 60 per cent of the patients who received a placebo had not been given a subsequent analgesic after 5 hours, this percentage was only 24 in Study 1419B and only 15 in Study 1425A. By the same token, the difference between placebo and aspirin 600 mg becomes much more striking in Study 1419B and 1425A than in Study 1419A. For example, in Study 1419A there was actually a higher percentage of patients remaining after 2 hours with placebo (96 per cent) than with aspirin 600 mg (87 per cent) and even after 5 hours the difference in favour of aspirin 600 mg was negligible (65 per cent compared to 60 per cent). In Study 1419B, the comparable differences between placebo and aspirin 600 mg were 40 and 77 per cent at 2 hours and 24 and 62 per cent at 5 hours. This affords an interesting foil to the fact that the t test and the multiple range test showed a statistically significant difference between placebo and aspirin 600 mg in Study 1419A, but not in Study 1419B. Apart from this one investigator’s tendency to give subsequent analgesics more freely with increasing experience, it is evident that the investigators concerned with Study 1422A and Study 1422B differed greatly in their judgement of the need for subsequent drugs.

This point perhaps requires emphasis. The question of how many doses of analgesic a certain type of patient is likely to need after surgery has constantly bedevilled the designers of clinical trials of this type (Swerdlow, Murray and Daw, 1963) and some previous experiences in Oxford in this respect have been reported (Parkhouse and Hallinon, 1967). Even in a constant environment, and without change of medical or nursing staff, variability is observed. The present authors were under the impression that all three investigators were applying much the same criteria for drug administration, and the importance of not withholding subsequent analgesics for the sake of the investigation was repeatedly stressed. If, despite this fact, such wide variations can occur there is clearly a need for extreme caution in attempting to compare opinions from different centres.

Throughout this investigation, drugs were of necessity given in fixed doses. It is not feasible to administer a solid preparation by mouth in graded doses according to the patient’s weight or some other predetermined characteristic. Among the 300 patients seen by the same investigator, mostly in the orthopaedic hospital, there was a wide range of ages and body weights and both sexes were represented. The multiple regressions shown in table IV were carried out in order to ascertain whether there was evidence that the degree of pain relief obtained from a given, fixed dose depends on age, weight or sex. These regressions were based on the investigator’s assessment, which was first of all compared (column 2) with the patient’s opinion. Agreement was so striking with all medications that it may be assumed that the conclusions reached in the subsequent columns, and indeed throughout the study, would be essentially the same whether patient’s or investigator’s assessment were used. In the case of the 300 mg and the 1200 mg dose there was a statistically significant relationship between the age of the patient and the response to the drug. Since there was no a priori reason to suppose that this relationship, if it existed, would be linear, the regression of response on the square of age was also computed; this showed a statistically significant relationship in the case of all three active medications. As would be expected, no relationship was shown in the case of the placebo. There was no demonstrable relationship between drug response and sex, or drug response and body weight. When more than one factor was taken into account in the regression, significant relationships were revealed wherever age was one of the factors, but not otherwise.

This regression analysis may be regarded as supporting evidence for the general clinical impression that older patients respond better to analgesics, or require smaller doses, than younger patients. It should be added that the mean body weights of the older and younger patients in each medication group were not appreciably different. The absence of a relationship between response
and body weight was a surprise, but seems unlikely to be an accidental finding. It indicates the need for further evidence, and for elucidation of the way in which this type of drug exerts its effect in relation to the pattern of absorption and distribution and the site of action.

The effect of food on aspirin absorption has been noted by several workers (Wood, 1967; Spiers and Malone, 1967). It has been shown that after a given dose of aspirin blood concentrations rise more slowly, and reach a lower peak, in non-fasting than in fasting subjects (Wood, 1967). The presumption is that since salicylates are absorbed more rapidly from the small bowel than the stomach (Gross and Greenberg, 1968) any factor which delays gastric emptying is likely to retard absorption. Acetylsalicylic acid is rapidly hydrolyzed to salicylic acid in the circulation, so that a slower rate of absorption would be expected to result in a lower peak level of unhydrolyzed drug which is probably the more potent form (Levy, 1965).

Although the present investigation was not specifically designed to study the effect of food intake, the time since the last meal was noted on all data cards. Taking Studies 1419A, 1419B and 1425A together, there was a sufficient number of comparable cases who had received each dose of aspirin to look for any obvious effect of recent food intake. A simple $\chi^2$ test was carried out, dividing patients into those who had eaten within 3 hours and those who had not. Pain was considered to have been relieved if a given total relief score was achieved, this level being set at 7 or more in order to have approximately the same number of cases in the relieved and not relieved groups. In the case of all four medications (that is, including placebo) the $\chi^2$ values were far below the level of statistical significance. Likewise, when all five studies were combined (using a relief criterion of 9 or more for Study 1422B and a criterion of 11 or more for Study 1422A) there was again no evidence of a relationship.

In this investigation the nurse-investigators made enquiry about the following side effects: headache, nausea, vomiting, other gastro-intestinal disturbances, coldness or clamminess, sweating, dryness of the mouth, palpitation, itching, skin rash, dizziness, sleepiness, tremor, restlessness, visual disturbance, auditory disturbance, other central nervous system disturbance, and genito-urinary disturbance. Respiratory depression was also noted if obvious. In each case provision was made for grading side effects as mild, moderate or severe.

In four of the five studies the occurrence of side effects was remarkably low.

In Study 1419A, vomiting occurred once with placebo (mild) and once with aspirin 1200 mg (moderate); sweating (mild) was noted once with

### Table V

Incidence of side effects with different medications in Study 1422B.
Numbers are numbers of patients and the severity of the reported side effect is indicated at the left.

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Other G.I.</th>
<th>Clamminess</th>
<th>Sweating</th>
<th>Dry mouth</th>
<th>Dizziness</th>
<th>Sleepiness</th>
<th>Tremor</th>
<th>Visual</th>
<th>Auditory</th>
<th>G.U.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>Mild</td>
<td>1</td>
<td>1</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mod.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
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<td>-</td>
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</tr>
<tr>
<td></td>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>300</td>
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<td>-</td>
<td>-</td>
<td>1</td>
<td>15</td>
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<td></td>
<td>Mod.</td>
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<tr>
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</tbody>
</table>
aspirin 1200 mg; sleepiness was noted twice (mild) with placebo, once (mild) with aspirin 300 mg, twice (once mild and once moderate) with aspirin 600 mg, and once (mild) with aspirin 1200 mg. In Study 1419B, the only side effect noted was one mild case of drowsiness with aspirin 1200 mg. In Study 1425A, moderate nausea was reported once with placebo and mild sleepiness once with aspirin 600 mg. In Study 1422A, headache (mild) occurred once with placebo; nausea occurred once (moderate) with placebo and once (moderate) with aspirin 1200 mg; vomiting occurred once (moderate) with placebo and once (moderate) with aspirin 1200 mg; itchiness was reported once (moderate) with placebo and once (moderate) with aspirin 1200 mg; sleepiness (moderate) was noted once with placebo.

In Study 1422B, side effects were reported much more commonly, and an analysis is given in table V. Once more, the difference between individual investigators is emphasized by this table. Despite attempts at a standardized approach, it is quite clear that some investigators will go to much greater lengths in seeking out side effects, will ask more leading questions and will read more into the patient's response, than others. In any group of investigations of this type the reported incidence of side effects may be expected to vary enormously, and herein lies a great difficulty in forming overall opinions of the value of a drug.

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REFERENCES


LA DOSE-RESPONSE CLINIQUE A L'ASPIRINE

Des doses graduées d'aspirine et un placebo furent administrés à un ensemble de 500 malades dans trois hôpitaux en vue de déterminer le degré de précision et de répétition susceptible de fournir un rapport dose-réponse. La sensation de douleur et de soulagement était subjective, des actions secondaires furent notées, et de nombreuses approximations en vue de l'analyse statistique des résultats furent utilisées. L'examen fut divisé en cinq études séparées; bien qu'une relation dose-réponse ressortit dans chaque étude, il existait une variation considérable, et les implications furent débattues.

DIE KLINISCHE WIRKUNGSDOSE VON ASPIRIN

ZUSAMMENFASSUNG