Drug treatment for acute upper gastrointestinal bleeding

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Tratamiento medicamentoso de las hemorragias agudas del tracto digestivo superior

SUMMARY

There is still much controversy about the value of drugs in the treatment of acute upper gastrointestinal bleeding, although many clinical studies have been performed.

In this review it is first discussed why these clinical studies have not yielded as yet unequivocal answers: many studies are not controlled or randomized, and often the studies are not double-blind. Comparative studies without placebo group are not valid as long as no drug has been proven to be undoubtedly efficacious. The number of patients included are often too small to allow any meaningful conclusion. Analysis of the data is not always done according to the standards accepted nowadays, e.g. analysis according to "intention to treat".

In the second part of this short review, the controlled studies published for the different classes of drugs are evaluated. It is clear that many of these studies suffer from the deficiencies mentioned above. Even for frequently used drugs such as H2-antihistaminics, vasopressin and somatostatin, convincing proof of their efficacy is not available.

RÉSUMÉ

En dépit des nombreuses études cliniques accomplies, une controverse demeure encore au sujet de la valeur des médicaments utilisés dans le traitement des hémorragies aiguës du tractus digestif supérieur.

Dans ce texte, nous avons d'abord discuté les raisons pour lesquelles ces études cliniques n'ont pas conduit à des réponses sans équivoque : de nombreuses études n'étaient ni contrôlées ni randomisées, et très souvent elles ne furent pas exécutées en double insu. Des études comparatives sans groupe placebo ne sont pas valables tant qu'aucune drogue n'a démontré une efficacité indiscutable. Le nombre de patients inclus dans les études sont insuffisants pour permettre une conclusion significative. L'analyse des données n'est pas toujours exécutée selon les standards acceptés actuellement, c'est-à-dire l'évaluation en fonction de « l'intention de traitement ».

Dans la seconde partie de cette courte revue, les études contrôlées publiées pour les différentes catégories de médicaments ont été évaluées. Il est clair que de nombreuses études souffrent des insuffisances mentionnées ci-dessus. Même pour des drogues très largement utilisées comme les inhibiteurs des récepteurs H2 de l'histamine, la vasopression et la somatostatine, la preuve convaincante de leur efficacité n'a pas été fournie jusqu'à présent.

RESUMEN

A pesar de numerosos estudios clínicos realizados, una controversia aún persiste alrededor del valor de los medicamentos utilizados en el tratamiento de las hemorragias agudas del tracto digestivo superior. En este texto, hemos discutido en primer lugar las razones por las cuales estos estudios clínicos no nos han conducido a respuestas de certeza: varios estudios no han sido controlados tampoco randomizados, y muchas no han sido realizados en doble ciego.

Estudios comparativos sin grupo placebo no son válidos, mientras no haya una droga que haya demostrado una verdadera eficacia. El número de pacientes incluidos en los estudios son insuficientes para permitir una conclusión significativa. El análisis de los datos obtenidos no está siempre hecho conforme a los métodos estándar actuales, es decir hacer la evaluación en función del "interés del tratamiento".

En la segunda parte de esta corta comunicación, los estudios controlados publicados por categorías diferentes de medicamento han sido evaluados. Es claro que numerosos estudios padecen de las carencias ya mencionadas. Mismo por drogas corrientemente utilizadas tal como son los aníl H2 de la histamina, la vasopresina y la somatostatina, la prueba convincente de su eficiencia no está dada hasta el momento.

Key-words: drugs, therapeutic trials, treatment, upper gastrointestinal bleeding.

Mots-clés : essais cliniques, hémorragie digestive haute aiguë, médicaments, traitement.

Palabras-clave : ensayo clínico, hemorragia digestiva superior aguda, medicamento, tratamiento.
There is still much controversy about the value of drugs in the treatment of acute upper gastrointestinal bleeding, although these drugs have been used for a long time, and many clinical studies have been performed. It is the purpose of this review to discuss why these clinical studies have not yielded unequivocal answers, and then to look more closely at the studies performed with the different classes of drugs available (Table I).

**TABLE I**

**CLASSES OF DRUGS USED IN TREATMENT OF ACUTE UPPER GASTROINTESTINAL BLEEDING**

- Antacids
- Histamine-H₂ antagonists
- Tranexamic acid
- Vasopressin
- Secretin
- Somatostatin
- Prostaglandins

**CLINICAL TRIAL METHODOLOGY**

The clinical trials of drugs for treatment of acute gastrointestinal bleeding do not always fulfill minimal criteria of quality [1].

- The studies have to be controlled, randomized and double-blind. The outcome after treatment with a putative therapeutic agent has to be compared to the outcome when patients are not treated with the drug under study. The outcome in patients with acute upper gastrointestinal bleeding (cessation of bleeding, need for surgery, death), is indeed unpredictable. The use of historical controls (i.e. comparison with the outcome in similar patients, in the same clinic, in previous years) is not valid. The decision whom to treat and whom not to treat with the product has to be taken by randomization. Double-blinding should be done whenever possible; otherwise, bias will influence the evaluation of the outcome.

- The studies should include a placebo group. Indeed, as will be discussed later, for none of the drugs is there unequivocal proof of efficacy and proving that a new drug treatment is «as good as» the old one, does not teach us whether, in fact, drug treatment affects the outcome. If one wants to compare two treatments, one should also include a placebo group.

- Large numbers of patients (and events) are needed. In fact, the number of events or endpoints, and not the number of patients included is important. This is illustrated by the following example. If a controlled study is carried out with 100 patients, and treatment with a drug is compared with treatment without that drug, with mortality as the endpoint, it will be much more difficult to show a difference if mortality is low than, if for the same number of patients, mortality is high.

- The inclusion criteria for the study should be strict. This is true first of all with regard to etiology: a drug could be efficacious in patients bleeding from peptic ulcer, and not in patients bleeding from varices. If patients of both categories are included in a study, an overall lack of effect of drug treatment does not exclude the possibility that in a subgroup of patients the drug could be of use. This is also true for age, severity of the disease and other factors which will affect prognosis. Stratification prior to entry in the study or evaluation per strata can be done, but conclusions will then be made on the basis of small subgroups of patients, with the difficulties inherent to small numbers, as mentioned before.

- Concomitant treatment should be standardized. Patients included in a study of drug treatment for gastrointestinal bleeding, will also receive other treatment (sclerotherapy, transfusion, general supportive treatment). The lack of standardization of concomitant treatment will decrease the power of the study to detect a real effect of the drug treatment.

- Endpoints should be clearly defined. This is mainly so for soft endpoints (such as rebleeding rates or transfusion requirements). Even if a hard endpoint, death, is used, one should define clearly within what time limit it should occur to be counted as related to the treatment.

- Finally, analysis of the data should be correct. There is more and more emphasis on analysis according to «intention to treat», where outcome is evaluated for all patients randomized to the study, whether or not they received the treatment under study.

As regard subgroup analysis, statistical tests to be used, intermediate testing etc., the general rules for clinical trials apply [1]. Finally it should be mentioned that there is a tendency to use «meta-analysis» in order to try to conclude whether treatment really helps [2]. It should be stressed that meta-analysis, i.e. trying to pool the results of individual trials, is only possible if the studies have been performed according to a correct protocol and if the studies are completely and correctly described.

In the discussion of the clinical studies of drug treatment in upper gastrointestinal bleeding which follows, it will become clear that many trials do not meet the minimal requirements listed above.

**RESULTS OF STUDIES WITH THE DIFFERENT CLASSES OF DRUGS**

**Antacids**

I could not find any studies of the use of antacids in the treatment of upper gastrointestinal