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BRIEF COMMUNICATION

PROPOSAL OF ABOLITION OF THE SKIN SENSITIVITY TEST BEFORE EQUINE RABIES IMMUNE GLOBULIN APPLICATION

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SUMMARY

An epizootic outbreak of rabies occurred in 1995 in Ribeirão Preto, SP, with 58 cases of animal rabies (54 dogs, 3 cats and 1 bat) confirmed by the Pasteur Institute of São Paulo, and one human death. The need to provide care to a large number of people for the application of equine rabies immune globulin (ERIG) prevented the execution of the skin sensitivity test (SST) and often also the execution of desensitization, procedures routinely used up to that time at the Emergency Unit of the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo (EU-UHFMRP-USP), a reference hospital for the application of heterologous sera. In view of our positive experience of several years with the abolition of SST and of the use of premedication before the application of antivenom sera, we used a similar schedule for ERIG application. Of the 1489 victims of animal bites, 1054 (71%) received ERIG; no patient was submitted to SST and all received intravenously anti-histamines (anti-H1 + anti-H2) and corticosteroids before the procedure. The patients were kept under observation for 60 to 180 minutes and no adverse reaction was observed. On the basis of these results, since December 1995 ERIG application has been decentralized in Ribeirão Preto and has become the responsibility of the Emergency Unit of the University Hospital and the Central Basic Health Unit, where the same routine is used. Since then, 4216 patients have received ERIG (1818 at the Basic Health Unit and 2398 at the EU-UHFMRP), with no problems.

The ideal would be the routine use of human rabies immune globulin (HRIG) in public health programs, but this is problematic, because of their high cost. However, while this does not occur, the use of SST is no longer justified at the time of application of ERIG, in view of the clinical evidence of low predictive value and low sensitivity of SST involving the application of heterologous sera. It is very important to point out that a negative SST result may lead the health team to a feeling of false safety that no adverse reaction will occur, but this is not true for the anaphylactoid reactions.

The decision to use premedication, which is based on knowledge about anaphylaxis and on the pharmacology of the medication used, is left to the judgment of health professionals, who should always be prepared for eventual untoward events.

KEYWORDS: Rabies; Equine rabies immune globulin; Anaphylaxis; Skin sensitivity test

An epizootic rabies outbreak occurred in 1995 in Ribeirão Preto, SP, with 58 cases of animal rabies (54 dogs, 3 cats and 1 bat) confirmed by the Pasteur Institute, São Paulo, and one human death. The Emergency Unit of the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo (EU-UHFMRP-USP), a tertiary reference hospital for the emergency care of a population from a geographical area of 1,000,000 inhabitants, and also a reference hospital for the application of heterologous sera, was faced by the need to provide care to a large number of people (with no disease!) for equine rabies immune globulin (ERIG) application. The occurrence of this new situation, together with the impossibility of predicting the extent and duration of the epizootic, made impossible the routine application of ERIG following skin sensitivity test (SST) as done previously[2,11].

In view of our positive experience of many years with the abolition of the SST before the intravenous application of antivenom sera (AVS) (because their low sensitivity and predictive value) and with the use of premedication, we decided to use an identical scheme for ERIG application[4]. Since we were convinced of the benefits of premedication as a safe measure for protection against possible and potentially serious reactions, we felt that we could not ethically conduct a controlled study, and all patients received the premedication according to the routine

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established in our service for AVS application: intravenous administration of antihistamines (anti-H1+ anti-H2) and hydrocortisone.

The immediate reactions that might occur with the use of heterologous sera may be mediated by IgE and can be detected by SST (anaphylactic reactions) or are triggered by complement activation, non-immunological activation of mast cells or of the modulators of arachidonic acid and do not depend on previous exposure to antigens (anaphylactoid reactions). These are not detected by SST[1,17]. The clinical manifestations of these two types of immediate reactions are similar, thus preventing inferences about the immunopathological mechanism involved.

In order to prevent or attenuate possible immediate reactions in risk situations, the use of anti-histamines (anti-H1 + anti-H2) and corticosteroids is recommended, with the latter acting as anti-inflammatory agent in the attempt to inhibit late manifestations of immediate hypersensitivity, reducing the continued release of inflammatory mediators, complement activation and vascular aggression, and having no immunosuppressive effect at the dose used[1,17].

A total of 1489 patients were seen at the EU-UHFMRP-USP from January to December 1995. Of these, 695 received only ERIG (because they had already received the first dose of vaccination before coming to the hospital), 359 received ERIG plus vaccination, and 435 were only vaccinated. The patients who received ERIG were kept under observation for 60-180 minutes and showed no adverse reaction. They were then referred back to their Basic Health Units of origin to complete the vaccination schedule and were instructed to return to the hospital if any complication should occur. The ERIG utilized were from 5 different sources: Butantan Institute (São Paulo), Vital Brazil Institute (Rio de Janeiro), National Health Institute (Colombia), Pasteur Institute (Paris), and Swiss Serum and Vaccine Institute (Switzerland)[5].

On the basis of the data obtained and in collaboration with the Municipal Health Secretariat of Ribeirão Preto, since December 1995 the application of ERIG has been decentralized and the patients from the city of Ribeirão Preto are instructed to look for the Central Basic Health Unit to receive ERIG. EU-UHFMRP-USP continues to be responsible for providing care to the patients coming from the 23 towns belonging to the Health Macroregion. The same routine was used at the two health units, e.g. use of premedication and without SST. From January 1995 to December 1999, 2398 patients received ERIG at the EU-UHFMRP-USP, and from December 1995 to December 1999, 1818 patients have received ERIG at the Central Basic Health Unit, for a total of 4216 patients. No adverse reactions have been observed.

With the use of purified ERIG the incidence of adverse reactions has been low (0.8%-6%), and most of those that occurred were minor, and relationated to local reactions and serum sickness[14,15,16]. The incidence of early manifestations is calculated to be less than 1:35,000 treatments[10]. Anaphylactic and anaphylactoid episodes have been reported to occur during desensitization or in patients with negative skin tests[7,15]. In Brazil, there are few reports of anaphylaxis among patients not submitted to SST or to premedication[3,6].

Recommendations for methods of administering skin tests and for its interpretation vary greatly. The standardization and validity of SST for predicting reactions to ERIG were discussed in a report on 150 patients with a positive SST who received ERIG without prior desensitization and under close supervision without problems[10].

The Report of WHO Consultation on Intradermal Application of Human Rabies Vaccines (1995)[12] recommends that the SST should no longer be used before ERIG, because there is no evidence that he predicts anaphylaxis or serum sickness reactions, suggesting instead direct serum application, with care taken to treat possible untoward effect. In 1997, the WHO[13] recommendation is that if the SST is positive, treatment with ERIG or preferably human rabies immune globulin should proceed if indicated, but special precautions should be taken if ERIG are used (e.g. pretreatment with adrenaline/epinephrine i.m. and with antihistamine) and the patient observed for at least one hour after the injection. Because techniques of skin testing have been not standardized the WHO recommends that national guidelines should be followed.

The ideal would be the routine use of HRIG in public health programs, but this is problematic, because of the high cost of HRIG. However, while this does not occur the use of SST is no longer justified at the time of application of ERIG, in view of the evidence of low predictive value and low sensitivity of SST involving the application of heterologous sera[4,10].

The administration of premedication is based on knowledge about the physiopathology of anaphylaxis and on the pharmacology of the medications used[1,8,17]. It is a process free from side effects and relatively inexpensive if we consider the time saved by the health professionals involved in the execution of the SST and desensitization (a painful, slow and not risk-free process)[9], in addition to avoiding discomfort to the patient. It is very important to point out that a negative SST result may lead the health team to a feeling of false safety that no adverse reaction will occur, but this is not true for anaphylactoid reactions.

The decision to utilize premedication is left to the judgment of health professionals, with the patient being kept under observation for 1 to 2 hours in any case, so that any adverse reaction may be immediately reversed.

RESUMO

Proposta de abolição do teste de sensibilidade cutâneo antes da aplicação do soro anti-rábico de origem eqüina

Durante o ano de 1995, ocorreu em Ribeirão Preto, SP, uma epizootia de raiva, com 58 casos de raiva animal (54 cães, 3 gatos, 1 morcego), confirmados pelo Instituto Pasteur, S. Paulo, e um óbito humano. A necessidade de prestar atendimento a um grande número de pessoas para aplicação do soro anti-rábico eqüino, tornou inviável a realização do teste de sensibilidade intradérmico (TSI) e da dessensibilização, utilizados até então como rotina, conforme orientação da Organização Mundial da Saúde e do Ministério da Saúde, na Unidade de Emergência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, hospital de referência para aplicação de soros heterólogos. Com base na experiência positiva de vários anos com a abolição do TSI e uso de pré-medicação antes da aplicação endovenosa de soros antivenenos, foi utilizado esquema semelhante para a aplicação de soro anti-rábico eqüino (SARE). Das 1489 vítimas de mordeduras de animais, 1054 (71%) receberam

SARE; nenhuma delas foi submetida ao TSI e todas receberam previamente anti-histamínicos (anti-H1 + anti-H2) e corticosteróides por via intravenosa, permanecendo em observação durante 60 a 180 minutos, não sendo verificada nenhuma reação adversa. A partir desses resultados, desde dezembro de 1995 a aplicação do SARE foi descentralizada em Ribeirão Preto, ficando responsável a Unidade Básica de Saúde Central (UBDS) pelos pacientes moradores da cidade de Ribeirão Preto, e a Unidade de Emergência do Hospital das Clínicas, pelos provenientes das cidades componentes da macroregião, utilizando-se a mesma rotina nesses dois locais, ou seja, abolição do TSI e uso de pré-medicação. Desde então até dezembro de 1999, 4216 pacientes receberam SARE, sem problemas (2398 na UE-HCFMRP e 1818 na UBDS).

O ideal seria a possibilidade de utilização de imunoglobulina anti-rábica humana nos programas de saúde pública, o que é problemático devido ao seu alto custo. Enquanto isso não ocorrer, a realização de TSI quando da aplicação de SARE não mais se justifica, devido às evidências do baixo valor preditivo e baixa sensibilidade dos TSI frente à aplicação de soros heterólogos. Mais importante ainda, um TSI negativo pode dar ao profissional de saúde a falsa segurança de que não ocorrerá nenhuma reação, o que não é válido para as reações anafilactóides.

A decisão da utilização de pré-medicação, que se baseia no conhecimento da fisiopatologia da anafilaxia e na farmacologia da medicação utilizada, fica a critério do profissional de saúde, que deve sempre estar preparado para eventuais intercorrências.

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