Pharmacological Treatment in Burns

PROCEEDINGS OF AN INTERNATIONAL SYMPOSIUM ON

Pharmacological Treatment in Burns

Milan, Italy

November 30 — December 1, 1968

Under the High Patronage of the President of the Italian Republic

Under the Auspices of The Italian Ministry of Health

Editors

A. Bertelli and L. Donati, Milan

1969

EXCERPTA MEDICA FOUNDATION, AMSTERDAM

INTERNATIONAL CONGRESS SERIES No. 190

Published December 1969

EXCERPTA MEDICA FOUNDATION OFFICES

Amsterdam	Herengracht 119–123
New York	New York Academy of Medicine Building, 2 East 103rd Street
London	Chandos House, 2 Queen Anne Street
Milan	Via San Senatore 6/2
Tokyo	Sankaido Building, 1-9-13 Akasaka, Minato-ku
Buenos Aires	Florida 165, Galeria Güemes, 4° Piso, Esc. 454/461

Printed in the Netherlands by Trio, The Hague.

Organizing Committee of the International Symposium on Pharmacological Treatment in Burns

Chairman

E. TRABUCCHI

President of the Italian Society of Clinical Pharmacology

Scientific Secretaries

A. BERTELLI

Institute of Pharmacology, University of Milan

L. DONATI

Institute of Plastic and Reconstructive Surgery, University of Milan

Scientific Committee

A. Bertelli (Milan), I. Clerici-Bagozzi (Milan), M. Dobrkovsky (Prague), G. Dogo (Padova), L. Gallone (Milan), A. Monsaingeon (Paris), G. Radici (Milan), S. Sevitt (Birmingham), E. Trabucchi (Milan), A. B. Wallace (Edinburgh)

The Symposium was Sponsored by

The International Society for Burn Injuries

The Italian Society of Clinical Pharmacology

Foreword

The problems caused by the potentially caustic agents which have been produced as a result of technological progress, not to mention the occurrence of natural disasters and the tragic incidence of war casualties, are giving rise to increasing concern.

While in the last few decades medical science has not always been very successful in its fight against burns, there has been a recent increase in possible methods of treatment of burnt patients.

In the past few years, many international meetings on burns have been held throughout the world dealing particularly with the surgical and clinical problems of treatment. A better knowledge of the biochemical aspects of burns, the identification of the physiopathological events correlated to shock, and the evidence of the key-role played by infectious processes, have enabled pharmacologists to prepare therapeutic agents for the treatment of burnt patients. But pharmacological research must be correlated with clinical results.

Research on burns has to be a field of encounter between biologists and surgeons, pharmacologists and clinicians. That is why the Società Italiana di Farmacologia Clinica has sponsored this interdisciplinary Symposium devoted to the pharmacological treatment in burns.

Our aim has been to make it possible to compare the results of different fields of research. The scientists from all parts of the world who participated in this Symposium have proved by the high scientific level of their work and by their active and enthusiastic collaboration that these aims were worthy of pursuit.

We hope very much that the scientific contribution made by this Symposium and the stimulating experience provided by discussion between scientists from different branches of medicine, will contribute to solving the social and medical problems posed by burns and will be fruitfully continued in future.

A. Bertelli

L. Donati

Table of Contents

III. ANTIREACTIONAL THERAPY

IV. CHEMOTHERAPY

I. Physiopathology

Chairmen:

E. TRABUCCHI, Milan

S. SEVITT, Birmingham

Contents

Studies on the reticuloendothelial system in burned rats with or without superimposed infections

L. JACQUES and A. MONSAINGEON

Hôpital Paul Brousse, Laboratoire de Chirurgie Expérimentale, Unité 17 de l'I.N.S.E.R.M., Villejuif, France

Risk of infection is still one of the most important problems in burned subjects.

Amongst the many natural factors which help to control bacterial invasion, the phagocytic activity of the reticuloendothelial system (RES) is of prime importance. The whole system acts as a diffuse organ, able to pick up within the reticular, endothelial and histiocytic cells, foreign material such as bacteria, carbon particles or vital dyes.

In burned animals, it is not yet known if the phagocytic activity of the RES is modified by the combination of the burn and infection which usually occurs some time before healing. Does superimposed infection by a known amount of bacteria – staphylococci or pseudomonas – interfere with the normal response of the reticuloendothelial system to the experimental burn?

METHODS

The RES activity is measured according to Halpern *et al.* (1950). After i.v. injection of a known amount of Indian ink (carbon particles of at least 10 Å, unable to pass through capillary membranes), the decreasing concentration of particles remaining in the plasma is measured by photometry. The disappearance rate is proportional to the phagocytic activity, mostly by the spleen and Kupffer's cells. Blood samples are taken, by transorbital route, 2 ½, 5, 10 and 20 minutes after injection. The phagocytic index is calculated: $K = \frac{\log C_1 - \log C_2}{T_2 - T_1}$, C being the concentration of Indian ink (mg/100 ml) at different periods of time between T_1 and T_2 (in minutes). In order to compare the different levels of activity according to the body weight and to the weight of liver and spleen, we use Stiffel's alpha index (Stiffel, 1957): $\alpha = \frac{P_c}{P_o}\sqrt[3]{K}$, in which Pc = body weight and Po = weight of liver + spleen.

The alpha index allows comparison between different series of animals. The slope of alpha (in semilogarithmic scale) against time (in minutes) measures the RES phagocytic activity in the different series of experimental animals.

Wistar rats were used; these weighed 200 grams at the beginning of the experiment. They were burned, injected and measured in series of 10 with standard diet, and water *ad libitum*.

Burns were made with an iron, 20 cm^2 surface area, at 80°C for 1 minute, on shaved and wet skin on the side of the animal. The burned area was about 10% of body surface.

Experimental infection was made by intravenous injection into the tail of a known amount of pathogenic bacteria in physiological saline.

The whole experiment included 13 series of 8 to 10 animals per series.

RESULTS

Each curve represents the average alpha index, constructed through 4 points, giving the mean activity of the 8 to 10 animals of each series.

There is no difference in phagocytic index between the two series of rats without superimposed infection: control animals and burned animals (during the first 48 hours after burning) have no significant difference of alpha ($0.70 < P < 0.80$) (Fig. 1). This result is in agreement with previous studies of Schimmel (1963), made in the same laboratory.

Superimposed infection, according to our hypothesis, could interfere with the phagocytic activity and some difference could be demonstrated between infected and non-infected animals.

1. Staphylococci infection, with or without burns

Control rats (*i.e.* not burned) were given i.v. 3.10^9 staphylococci (coagulase +). The Indian ink injection was made 48 hours or 96 hours after this experimental infection. The alpha index significantly increases (8.8 compared with 5.9 for controls) after 48 hours. The index was only 7.3 after 96 hours (P between 0.02 and 0.05). 15 days later the index was still somewhat increased but the difference compared to control animals was not significant.

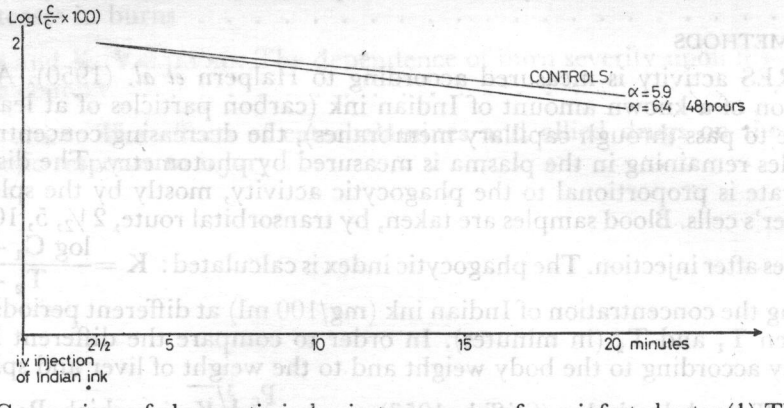

Fig. 1 Comparison of phagocytic index in two groups of non-infected rats: (1) The controls and burned animals; (2) The amount of Indian ink injected was 8 mg/100 g of body weight. The measurements of Indian ink concentration in the blood were made 2½, 5, 10 and 20 minutes after i.v. injection.

It seems, therefore, that the RES response is much more active 2 days after infection than later (Table I and Fig. 2).

In burned rats (burning and infection procedures being made simultaneously), the same kind of experimental infection with the same amount of the same staphylococci was made and the phagocytic index measured at the same intervals of time.

TABLE I

	Controls	Non-burned rats infected by 3.10^9 staphylococci (i.v.)		
		48 hours	96 hours	15 days
		post infection		
Alpha	5.9	8.8	7.3	6.6
Std deviation	± 0.21	± 0.27	± 0.42	± 0.15
P		0.01	0.02–0.05	0.30–0.40

After 48 hours, the alpha index significantly increased compared with control animals (7.6 instead of 5.9) but much less than in rats which were not burned. At 96 hours, there was no difference. At 15 days a not significant difference existed (Table II and Fig. 2).

It should be emphasized that this experimental infection was always tolerated by animals provided that the burned surface was below 20% of body surface (Schimmel, 1963).

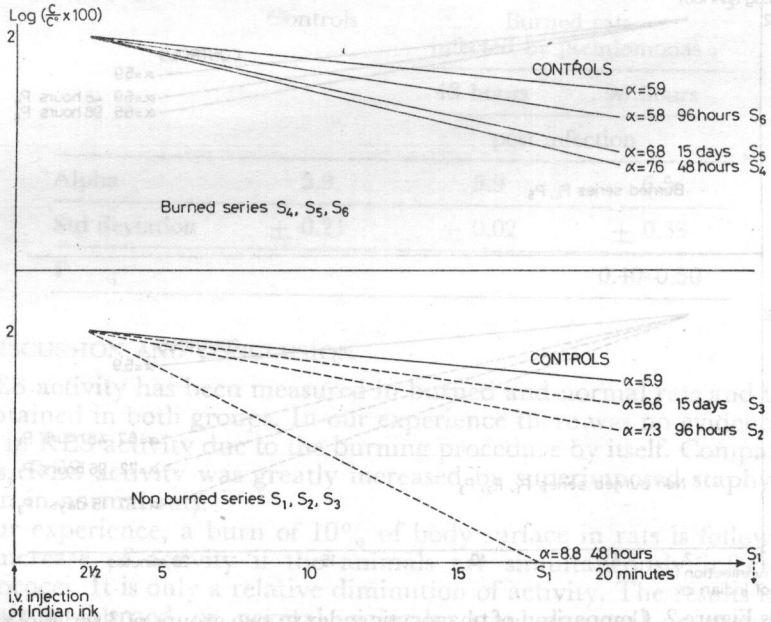

Fig. 2 Comparison of phagocytic index in two groups of 3 series of rats with controls. The rats were injected with 3.10^9 staphylococci. The Indian ink tests were made:
48 hours after burning and infection .... S_4
96 hours after burning and infection .... S_6
15 days after burning and infection .... S_5
In the non-burned series, the tests were made in similar conditions:
48 hours after infection .... S_1
96 hours after infection .... S_2
15 days after infection .... S_3

TABLE II

	Controls	Burned rats infected by 3.10^9 staphylococci (i.v.)		
		48 hours	96 hours	15 days
		post burn and infection		
Alpha	5.9	7.6	5.8	6.8
Std deviation	± 0.21	± 0.12	± 0.30	± 0.25
P		0.02–0.05	0.9	0.10–0.20

2. *Pseudomonas infection, with or without burns*

Non-burned rats were given i.v. 1.10^9 *Pseudomonas aeruginosa*. When the alpha index was measured 48 or 96 hours later, the increased activity was not significant; at 15 days, the alpha index was 7.7 (5.9 for controls) and the difference significant, P = 0.02 level (Table III and Fig. 3).

Burned rats given the same amount (1.10^9 *Pseudomonas aeruginosa*) at the same

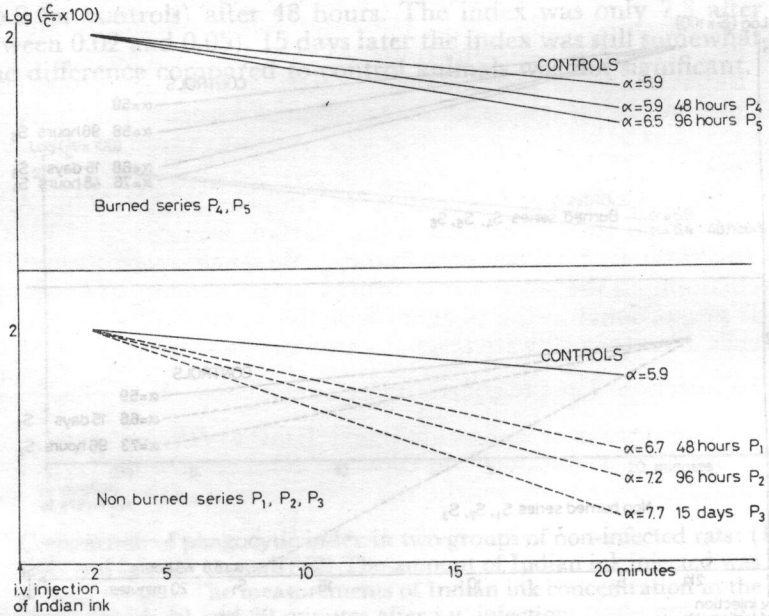

Fig. 3 As Figure 2. Comparison of phagocytic index in two groups of 3 series of rats with controls. The rats were injected with 1.10^9 pseudomonas. The Indian ink tests were made:
48 hours after burning and injection .... P_4
96 hours after burning and injection .... P_5
In the non-burned series, the tests were made in similar conditions:
48 hours after injection .... P_1
96 hours after injection .... P_2
15 days after injection .... P_3

TABLE III

	Controls	Non-burned rats infected by 3.10^9 pseudomonas		
		48 hours	96 hours	15 days
		post infection		
Alpha	5.9	6.7	7.2	7.7
Std deviation	± 0.21	± 0.16	± 0.40	± 0.16
P		0.20–0.30	0.10–0.20	0.01–0.02

time as burning (10% of body surface), had the same alpha index as the controls at 48 hours, with a low standard deviation. There was no significant increase at 96 hours. The following lethality does not permit evaluation of the alpha index 15 days later (Table IV and Fig. 3).

TABLE IV

	Controls	Burned rats infected by pseudomonas	
		48 hours	96 hours
		post infection	
Alpha	5.9	5.9	6.5
Std deviation	± 0.21	± 0.02	± 0.39
P			0.40–0.50

DISCUSSION AND CONCLUSION

The RES activity has been measured in burned and normal rats and the same level obtained in both groups. In our experience there was no evidence of any change in RES activity due to the burning procedure by itself. Compared with controls, RES activity was greatly increased by superimposed staphylococcal infection in normal rats.

In our experience, a burn of 10% of body surface in rats is followed by a lower increase of activity if the animals are simultaneously infected with staphylococci. It is only a relative diminution of activity. The results in all the experiments (burned or normal animals; staphylococcal or pseudomonas infection; early or late Indian ink test) have never shown any decrease in the phagocytic index when compared with controls. The curves have never suggested a true depression of RES activity.

Increased activity was greatest in early stages and diminished later, but may still be present after 15 days.

A burn (10% of body surface) combined with the same staphylococcal infection interfered with the RES activity which seemed less increased than without burn. In normal rats pyocyanic infection, in our experimental conditions,

did not increase RES activity in comparison with controls until 15 days after infection.

Burned animals (10% of body surface) showed the same alpha index as non-infected normal animals.

ACKNOWLEDGEMENT

The authors are indebted to Pierre Trafton and Chantal Delain for their efficient help.

REFERENCES

HALPERN, B. N., BIOZZI, G. and BENACERRAF, B. (1950): Technique d'étude quantitative de l'activité granulopexique du système réticulo-endothélial. *C.R. Soc. Biol. (Paris)*, *144*, 232.

JACQUES, L. and MONSAINGEON, A. (1967): Infections à *Pseudomonas aeruginosa* chez les brûlés (bactériémie expérimentale à bacilles pyocyaniques chez les rats). (Travail de l'Unité 17 de l'I.N.S.E.R.M.). *Bull. Inst. nat. Santé Rech. méd. (Paris)*, *22/1*.

MONSAINGEON, A. (1968): Communication: Des risques septiques dans la chirurgie moderne. XXII Congrès de la Société Internationale de Chirurgie, Vienne, 4-8 Sept. 1967. *J. roy. Coll. Surg. Edinb.*, *13*, 200.

SCHIMMEL, H. (1963): Bactériémie expérimentale à staphylocoques chez le rat. Utilisation d'une technique d'empreintes sur milieu solides. *Ann. Inst. Pasteur*, *104*.

STIFFEL, C. (1957): *Etude de la Fonction Phagocytaire des Cellules du Système Réticulo-Endothélia au Contact du Sang*. Thèse Doctorat ès-sciences naturelles, Paris.

Prevention of thrombo-embolism in burned patients by oral anticoagulant therapy

S. SEVITT

Pathology Department, Birmingham Accident Hospital, Birmingham, United Kingdom

During the last ten years in the Birmingham Accident Hospital a course of oral anticoagulant therapy with an indane-dione or coumarin drug has been given to many patients with burns covering less than 10% or 15% of the body area in order to prevent deep vein thrombosis and pulmonary embolism. The purpose of this paper is to outline the need for this prophylaxis and the reason why it is confined to those with relatively restricted burns.

Pulmonary embolism is a serious hazard after accidents, after surgery and after various medical conditions and is not uncommon in burned patients. Unfortunately, embolism is often unsuspected or difficult to diagnose so that clinical data greatly underestimate its incidence. Routine necropsy studies showed major pulmonary emboli in 9 out of 163 subjects (5.5%) who died after burning as well as a high incidence of embolism (20%) in other injured subjects (Sevitt and Gallagher, 1959). Most of these cases were unsuspected during life. The emboli arise from thrombi in the deep veins of the lower limbs and pelvis and long ilio-femoral thrombi are particularly dangerous. Necropsy data obtained by opening the lower venous tree showed deep vein thrombi in 20 out of 33 burned patients (60%). Deep vein thrombi were also found in 66% of 92 other injured subjects who reached necropsy. Most of those with deep venous thrombi had no symptoms or signs referable to the lower limbs. This *silent* thrombosis is the explanation of *unheralded* embolism. Differences in the frequencies of thrombosis and embolism at necropsy were observed in different groups of burned and injured patients, and the differences were largely dependent on the duration of bed rest preceding death and on the age of the subjects. Venous thrombosis was infrequent in those who died within a few days of injury and became more frequent in those who survived longer, especially among middle-aged and elderly subjects. In these patients survival-time is equivalent to bed rest and this supports the importance of venous stasis in the genesis of deep vein thrombi. The rate of thrombosis was particularly high in those over 40 years of age who survived longer than three days of bed rest, and in younger subjects with bed rest longer than a week or two. Such patients provide the great majority of cases of embolism. This was found to be important in the selection of groups of subjects for prophylactic anticoagulant therapy.

It is noteworthy that the nature of the injury has little direct influence on the incidence of thrombosis; its influence is indirect and is mediated through age, duration of venous stasis (bed rest or otherwise) and prolongation of life