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Problems Associated with the Preparation and Use of Intravenous Fluids

John Ocran, B Pharm., Ph. D., M.P.S.G.[1]

Some pharmaceutical products are so simple in composition that it appears anybody can make them. One such group of preparations are the intravenous fluids. After being told that normal saline contains 0.9 per cent w/v Sodium Chloride there is the temptation for the nurse, the assistant in the dispensary or the medical practitioner to think that he can make normal saline injection himself therefore does not see the need for or importance of the pharmacist. It may be relatively easy for anybody to prepare say 100 ml of normal saline injection but when it comes to preparing fairly large quantities e.g. 100L of the same solution, as one may well do in a busy hospital dispensary, the associated problems become so complex that only a well trained pharmacist can handle them.

In this case, it would be necessary to evolve a procedure which ensures effective dissolution and mixing making use of the apparatus and facilities available. It would also involve testing the solution for homogeneity. Various methods of distributing the solution into the final containers and handling the containers will have to be examined and assessed to determine which is most efficient in use of equipment, space, manpower and time bearing in mind the accuracy and/or quality required in the preparation.

Having established a routine effort should be made to ensure its continuing efficiency and faithfulness with which it is followed by the operators.

PYROGENS

The first problem that should be tackled concerns water. The need for pyrogen-free water cannot be over emphasized so it is essential to find out if the still being used produces apyrogenic water. Since most dispensaries will not have the facilities for carrying out the test for pyrogens, this will mean getting a reputable laboratory to perform the rest. The next problem which arises is how to transport the water from the still to the point of use without the possibility of the production of pyrogens or microbial contamination before the water is used. It is not only the water which should be apyrogenic but also the solid, that is sodium chloride. Even if the source of supply of sodium chloride does not change one cannot guarantee that after one batch has passed the pyrogen test subsequent batches will be apyrogenic.

[1] Faculty of Pharmacy, University of Science & Technology, Kumasi.

When dealing with such large quantities it is difficult to ensure effective dissolution and mixing of solutions, neither it is easy to distribute the solution into the final containers in a manner which excludes particulate and/or microbial contamination of the contents. How does one convince himself that the sterilization process to which the product is subjected guarantees the sterility of every individual container? Finally is the problem of subjecting the product to an examination which guarantees its suitability for use with regard to particulate content.

It should be realized that an unsatisfactory solution to any of the problems which come up during the production means increased probability of the preparation becoming pharmaceutically unacceptable.

With all the limitations of the official sterility test one can still make a reasonable decision as to whether a batch of preparation is sterile or not. The same can be said of the other desirable characteristics-homogeneity, limits of content of active or dissolved substance and apyrogenic nature.

PARTICULATE MATTER

However, there is no guide whatsoever, official or otherwise, as to what constitutes an acceptable preparation as far as the particulate content is concerned and one is left to use his common sense which makes the decision rather controversial. The rest of the paper will therefore be devoted to a discussion of this problem which was neglected until quite recently when the detection of solid particles was made relatively easy by the introduction of suitable instruments. It should be realized that irrespective of the undesirable nature of the particles and the process through which the solution is passed some particles will inevitably be present in the final product. The problem therefore is "how many particles of what size and nature (chemical) make a product unacceptable?" In the absence of any guidance in either the pharmaceutical or medical literature the only course left for the pharmacist is to rely on his conscience and knowledge of what is Practicable perhaps by reference to material produced by reputable manufacturers. As suggested by Goddard (1966) it may be possible sometime to come to use instrumental counts to determine the acceptability or otherwise of a solution. Before this becomes generally accepted the pharmacist must have an idea about the sources of particulate contamination so that special effort can be made to reduce the number in the final solution to the barest minimum. Armed with a good knowledge of the chemical nature of the particles the number and size likely to cause trouble and the possible dangers to the patient he will be in position to make reasonable decisions concerning his preparations.

Sources and Chemical Nature

Particulate matter present in parental solutions may originate from (a) materials present in the final container which have not been removed during washing prior to filling; (b) materials present in the solution and not removed during clarifications; (c) particles falling by chance from the atmosphere into the final the container during the filling operation; (d) particles shed by glass surfaces in contact with the saline solution for prolonged periods of time; (e) rubber or plastic closures in contact with the solution, especially, if the solution has been heat sterilized; (f) particles shed from the filter medium itself. Garvon and Gunner (1963, 1964,

1971) have reported that they identified some of the solids present in commercial injection solutions as carbon black, whitening, zinc oxide and clay. These workers concluded that the particles originated from the rubber-closures since the particles were present representative of materials commonly used as fillers in rubber. They also showed that blisters on the surface of a rubber closure could rapture during heat sterilization, and blamed rubber closures for the majority of cellulose fibres found in the solution. However, rubber closures cannot be the usual sources of fibres since solutions packed in all glass or all plastics containers also contain fibres. It has been suggested by Fowler (1959) and by Endicott **et al** (1966) that chance contamination from the environment during the filling operation is the main source of this type of material.

If it is accepted that rubber closures are a possible source of contamination will be greatly reduced if this type of closure is avoided or if it is improved by coating the surface with a suitable inert lacquer. The improvement by coating may not however eliminate the possibility of particles being pushed into the solution by the syringe during use. However, where the same solution has been packed in tan all-plastics container and a rubber closed bottle the former has been found to give a lower particle count; Groves (1966).

Since a large particle will almost certainly block the needle used to administer the infusion it is fairly easy to state the upper limit of size of particles to be found in intravenous solution. Particles of diameter around 300um are likely to block a No. 18 gauge hypodermic needle but no standard can be set regarding the smallest particles that should be tolerated. Again, it is extremely difficult to prescribe a limit for the number of particles since each individual particulate contaminant is potentially capable of causing a reaction in the body. Perhaps the only way of preventing particles from entering the patients blood stream is by inserting a membrane filter at the end of the giving set.

Dangers to Patient

The probable consequence of administering large quantities of pyrogenic solutions heavily contaminated with micro-organisms are too well known to be discussed here. Non-homogeneity in the batch may mean giving hypotonic solutions to some patients whilst others receive hypertonic solutions both of which may produce disastrous results. Thus one does not have any problem in deciding whether to reject or accept a batch of intravenous fluids when it does not meet the standards of homogeneity, absence of pyrogens and sterility, knowing very well the dangers involved in using such solution. In the case particulate contamination the pharmacist is in a dilemma because added to the problem of deciding what size, number or type of particle he should permit in the solution he can only speculate on the possible dangers to the patient after deciding to accept a given batch.

The chemical nature of the particle may be crucial in determining the effect a particle may particle may produce. In some cases the particle may not produce any biological effect at all but the possibility of inciting an inflammatory, neoplastic or antigenic response cannot be ruled out. The particle which does not produce any of the above responses is still dangerous potentially since it may block the lumen of a blood vessel. The question which arises is “where is the particle likely to lodge?”. A particle injected into a radial vein of the arm is not likely to

come to rest in a vein as it travels along the veins of increasing diameter towards the heart. After passing through the heart and pulmonary artery the chances of the particle blocking an artery increase as the diameter of the branching arteries decrease away from the heart. The diameter of the finest capillaries being about 5.1 um it is perhaps reasonable to say that as far as possible, particles above the size should not be permitted in intravenous fluids so as to reduce the risk of occlusion of the arteries. The effect of occlusion will be determined by the availability or otherwise of alternative circulation to the tissue. If the occluded vessel happens to supply an organ which does not have many alternative pathways for the blood e.g. kidneys or brain, then the result may be permanent damage. It may be argued that the pulmonary venous circulation, where occlusion will be less dangerous, can act as an effective filter unit and prevent large particles from reaching the systemic circulation. Prinzmetal and co-workers (1948) have shown that glass beads as big as 390um could pass through the lungs and reach the systemic circulation. The above discussion shows that the pharmacist cannot take any chance over particulate contamination in intravenous fluids since it is his primary responsibility to help save life and not endanger it. At the moment there is no way of ensuring that the solution is completely free from particles of any size but if the pharmacist will personally take charge or supervise the preparation of such solutions and select the right packaging materials, he can satisfy himself that he has done everything within his ability to produce the best possible solution.

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