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The Toxicity and Safety Testing of Disposable Medical and Pharmaceutical Materials*

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Many disposable surgical and pharmaceutical materials are not adequately tested for their toxicity and compatibility with tissues. Suggested techniques are described for testing these items. By the use of such tests the various items available may be checked and a choice made between those which should not be used and those which have been adequately tested and are found to be satisfactory.

Because of high labor cost and an inadequate supply of properly trained personnel, the demand for disposable, ready-to-use medical and pharmaceutical materials has resulted in the introduction of many such items in the commercial market. Disposable syringes, needles, vials, catheters, drain tubes, and countless other items are now available. For the most part these are made of plastic or one of the newer, lighter weight alloys. Many of these items offer advantages over the original re-usable item. The throw-away hypodermic needle, for instance, cannot transfer infectious hepatitis from one patient to another, and, since the needle point does not have to withstand repeated injection, it can be made much sharper. More care can be given to its sterilization in autoclaves or gas sterilizers with the proper controls than by the busy physician with an office sterilizer. Also, the individual needle can be sealed in the final package before sterilization, and it maintains sterility until the time of use.

Other disposable items have similar advantages over the original re-usable ones. By changing the plasticizers or other chemicals in the plastic formulations, catheters may be made with any flexibility desired. From a pharmaceutical point of view, bottles and pharmaceutical "glassware" which will not break have many advantages. The pharmacist must take care, however, in the use of these materials, since some of the plasticizers may be leeched out and react with the drugs stored in them. Or they may be permeable to, or soluble in, the solvents which they contain.

The individual plastic or alloy formulations must be carefully tested by chronic and acute testing methods before being employed. Tests which simulate actual conditions of use should be employed, with added tests to give a large degree of safety.

The responsibility of the manufacturer does not end with the careful checking of the original formulation, but tests on each individual lot must be performed, since plasticizers, coloring agents, and plastics may change from lot to lot without the manufacturer's knowledge.

The Food and Drug Administration has been very interested in those plastic formulations used for food containers, and a number of publications have appeared stating which plasticizers and other substances may or may not be used for such items. This has led to some false sense of security on the part of the surgical suppliers; they felt that since their formulations met these requirements that they were entirely satisfactory and met all the requirements for medical use. A great deal of harm may have been done by the labeling of some plastic tubings as medical grade tubing, without adequately testing the material by imbedding samples in animals. Drains and indwelling catheters made from some of this material cause tissue reaction and necrosis which is open to bacterial infection.

Although the U. S. P. has certain sterility and toxicity requirements for plastic tubing assemblies used in blood collection and transfusion, no such requirements or tests are outlined by either the U. S. P. or FDA for tubing to be used for drains or indwelling catheters.

One has only to recall the reports in publications of the AMA on reactions to improperly tested plastic formulations used in watch bands, belts, etc., to understand how much more important is the adequate testing of plastics for surgical and medical use.

Several years ago the authors were asked by a firm, which was planning to manufacture a plastic-hubbed hypodermic needle, to develop toxicity and safety tests for this item. The procedure devised would be used to determine whether the plastic formulations, which met their physical specifications, would also prove nontoxic under all the uses to which needles would be subjected. Several arbitrary tests were developed; some

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actually simulated conditions of use and others were developed to give a margin of safety. It was found that a few coloring materials could not be used since they would leech out on long contact with saline, which might occur during use. Some formulations were found to be toxic and could not be used. In like manner, some plasticizers were found to be unsatisfactory.

TEST PROCEDURES

The specific tests which are applied to needles are as follows: Each needle hub formulation is checked, using the following solvents: 0.9% saline, 5.0% ethyl alcohol, sesame oil, and polyethylene glycol, since these would represent the most common solvents used in parenteral products. Not less than 20 needles are covered with each of the above menstrua, 1.5 ml. per needle. The overlay preparations, along with control portions of the four solvents, are held at 37° for eighteen to twenty-four hours. The eluates are decanted after vigorous agitation to aid elution of possible surface reaction products. The following tests are then performed:

Acute Toxicity.—Fifteen healthy mice, weighing 18–22 Gm., are injected with each of the menstrua, paralleled by five mice using the control solutions. The saline and ethyl alcohol eluates are injected intravenously, 1.0 ml. per mouse. The sesame oil and polyethylene glycol are injected intraperitoneally, 1.0 ml. per animal of the first, while a dilution of the polyethylene glycol is used which is just below the level causing toxic manifestations in previous control studies. The animals are observed for seventy-two hours.

Bleb Reactivity.—Each of the four elution menstrua is injected intracutaneously, 0.2 ml. into each of ten sites, paralleled by ten 0.2-ml. control blebs in the backs of two rabbits. The first three are injected undiluted, while the polyethylene glycol is diluted to contain 20 mg. in the 0.2-ml. bleb volume. The sites are observed for seventy-two hours for erythema, edema, or necrosis.

Pyrogenicity.—Ten needles are heated in 200 ml. saline to not less than 85° for one hour and the U. S. P. pyrogen test on the decanted eluate performed.

After the original formulation study, production control tests are run, using the saline overlay only.

To simulate actual conditions of use, as in dermatological work, needles are attached to a small syringe and 0.25 ml. saline is drawn into the syringe, leaving the needle cannula filled. These are placed in a tray and held twenty-four hours at 37°, and then blebs raised on a rabbit. Since only a very small area of the inside of the hub is actually in contact with the solution, one might never expect to obtain any toxic reaction. In this manner it has been possible to observe toxicities on some of the formulations discussed above.

OBSERVATIONS

Although these tests were designed for plastic hubs, some interesting findings were noted when experimental lots of aluminum hub needles were submitted to these tests. At first it was not thought necessary to test an all metal needle for toxicity, since no plasticizers or epoxy resins were involved. Since it was known that some of the alloys used contained a small amount of lead to facilitate manufacture, we decided to submit these needles to the same test. A floccular precipitate developed in the saline, and on intravenous injection into the mice killed all of the ten mice within a few minutes. When this floccular material was submitted to the bleb type of test, all the test sites gave positive skin reactions.

These sudden deaths and positive skin tests could not possibly be due to the small amount of lead eluted from these hubs since less than 1 mg. of weight loss occurred during the saline soaking. The deaths must be due to embolism of the floccular material which occurs with aluminum and saline. These tests were repeated with distilled water, and only a slight haze was seen. However, when this material was made isotonic with sodium chloride for intravenous injection, the floccular precipitate developed and death resulted in the mice, although not to the same extent since the amount of precipitate was not as great. No deaths occurred when this material was given intraperitoneally or when the experimenter was very careful not to disturb the precipitate and only injected the supernatant liquid.

This type of safety test does not simulate actual conditions of use since the entire surface area is in contact with the solution. In the actual use type of test in which the needles were placed on the syringe and 0.25 ml. saline drawn into the syringe and allowed to stand, as might occur in a dermatologic clinic where large numbers of allergens are being tested, positive skin tests did occur in the blebs raised on the rabbits, provided the material was mixed by shaking and the precipitate which formed expelled. To determine whether or not this material might also cause false positive reactions in humans, dermatologists repeated these tests, making sure that they mixed the material before injection. About 40% false positive reactions on two series of tests employing this technique were obtained. The number of reactions in the animals and humans is proportional to the amount of precipitate which is injected. If the syringe is handled very carefully so that most of the precipitate remains in the syringe, fewer positive reactions will result.

From the point of view of the hospital pharmacist or laboratory technician, aluminum-hubbed needles should not be used on a pitkin or other type dispensing syringe, which is placed back in the flask of saline each time in order to fill it and then remains in the saline. When used in blood grouping or other tests employing washed red cells, the small amount of aluminum eluted may cause agglutination of the red cells and lead to erroneous results. This finding was noted by one of the blood banks that was using saline from a bottle to which an aluminum needle was attached and which remained in contact with the saline for a long period of time.

For disposable syringes a slightly different technique must be employed in testing. Each syringe formulation is studied, using the solvents discussed under needle testing. With the syringes, the barrels of 20 units are filled with the solvent and allowed to warm to 37° for twenty-four hours. The eluates are then combined and tests for acute toxicity and

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Fig. 1.—Subcutaneous implant: seventy-two hours, no reaction.

Fig. 2.—Subcutaneous implant: seventy-two hours, showing reaction.

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Fig. 3.—Intramuscular implant; seventy-two hours, no reaction.

Fig. 4.—Intramuscular implant; seventy-two hours, showing reaction.

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bleb reactivity simulating those for the needle eluates are performed.

Plastic syringe plungers and rubber plunger tips are studied by elution, in much the same manner as described above for needles, except that 10 Gm. of the test material may be covered with 50 ml. of the elution menstruum rather than by using 20 test items.

Control testing of approved formulations in syringe assemblies is performed by drawing 1.0 ml. of 0.9% saline into the syringe plus 1.0 ml. of air, and eluting the assembly for eighteen to twenty-four hours at 37°. Twenty units are so eluted and the eluates combined for acute toxicity and bleb reactivity tests.

Other plastic items: indwelling catheters, drains, stomach tubes, intravenous feeding tubes, and tubing for general medical use are also tested. Plastic formulations developed for use in contact with body tissues, especially where the normal epithelium has been interrupted, are tested for acute toxicity, bleb reactivity, tissue reaction, and pyrogenicity.

Ten grams of the material is cut into relatively small pieces and covered with 50 ml. of sterile 0.9% saline; a like preparation is made using 5.0% ethyl alcohol. These overlays are then warmed to 37° for twenty-four hours, along with control portions of the two menstrua. The overlays are then vigorously shaken and the elution menstruum decanted.

Acute toxicity is determined by injecting the undiluted eluates and control solution in doses up to 1.0 ml., both intravenously and intraperitoneally, in mice weighing 18–22 Gm. This is equivalent to injecting the eluate from 10 Gm. of the plastic per Kg. of body weight.

Bleb reactivity is determined in a manner simulating that described above under needle testing.

Tissue reaction or toxicity exhibited by the tissues in contact with the plastic material is studied by implanting sections roughly 1.5 × 10 mm. in size subcutaneously and intramuscularly in the rabbit. At least four such sections are implanted subcutaneously, paralleled by four known nonreactive controls; a like number are implanted intramuscularly in a second animal. The implants are allowed to remain in place for seventy-two hours, after which the animals are sacrificed and the implant sites examined for surrounding reactive material. The acute, seventy-two-hour tests are evaluated by careful gross examination only. Those formulations which pass the acute implant tests and which may be in contact with the body tissues for a longer period of time are also implanted for sixty-day periods. These implant sites are then evaluated by gross examination and histologically by a competent clinical pathologist. Likewise, those formulations likely to be used in contact with the central nervous system are implanted for seventy-two hours and sixty days in the cerebral cortex of the rabbit for careful evaluation. The implantation procedure has proved to be the most useful of the tests devised to determine tissue compatibility of a plastic formulation.

Pyrogenicity is studied by heating 10 Gm. of the formulation in 200 ml. of saline to not less than 85° for one hour, and subjecting the eluate to the standard U. S. P. pyrogen test procedure.

When a number of the medical grade tubings were tested, some were found to be entirely satisfactory and produced no reaction in contact with the tissues, as shown in Figs. 1 and 3. Other samples of tubing produced a very severe reaction, as shown in Figs. 2 and 4.

SUMMARY AND CONCLUSIONS

It is felt that before use of any material which may produce pathological conditions, that unless there is proof that such testing has been done on each lot produced, similar tests on each lot of material purchased should be run.

As stated above, some of these tests are severe and do not simulate actual conditions of use, but were designed to give a margin of safety. They may also explain some of the reactions which have been encountered in the use of these "throw-away" type products which, until now, could not be accounted for.

It is realized that the tests described are not ideal for all of the different disposable items available. The purpose of this paper is to stimulate the hospital pharmacist or other persons responsible for the purchase of disposable medical supplies to make sure that adequate sterility and toxicity testing has been performed, and that the items are satisfactory for the purpose for which they are to be employed.

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