EFFECT OF INHALATION OF LOW DOSE METHYL METACRYLATE VAPOR ON THE CNS SYSTEM OF RATS

SAIME SAHIN*
MÜJGAN ÖKTEMER*
SEVGI KÜLLÜ**

SUMMARY: In this research, histopathological examinations of central nervous system of the rats, exposed to low concentration (0.45 ppm) of methyl metacrylate monomer (MMA) vapor, were made.

60 male Swiss Albino rats (30 experimental, 30 control) were exposed to MMA vapour in air for period of 4, 8 and 12 weeks, 5 days per week and 1 hour per day. The concentration used was determined by measuring the air in a dental laboratory during the acrylate mixing phase.

As a result in four and eight week groups significant pathologic changes were leptomeningeal thickening, mononuclear cell infiltration, ependymitis and ventriculitis. Leptomeningeal thickening and mononuclear infiltration were observed in two-third of the 12 week groups but were less pronunced than that of in eight week groups.

In conclusion, MMA vapour was found to have a toxic effect on central nervous system. The results shown us the importance of the ventilation of the places in which MMA is worked with.

Key Words: Methyl Metachylate Vapour, CNS System, Histopathological Examination.

INTRODUCTION

Methyl metacrylate polymer is a substance which is commonly used in all branches of dentistry, and because of its similar properties to bone it is further used in many areas of medicine. In orthopedic surgery it is used to make artificial knees and shoulder joints, as a ground substance to join orthopaedic prostheses together, and as a filling substance to repair defects in the skull or vertebrae. It is also used in the manufacture of eye prostheses. In all of the above uses the methyl metacrylate comes into contact with living tissue.

Nowadays this polymer has also found uses in many areas of industry. With such a wide use of methyl metacrylate monomer, and given doubt as to its safety, research into possible toxic effects is currently being performed.

There are many reports corcerning side effects encountered during medical use. These side effects include contact dermatitis (7,8,18), allergic stomatitis (9), and respiratory (4) and cardiovascular distrubance (6). Cardiovascular effects are highly varied and include profound hypotension, cardiac arrythmias (1, 15), coronary artery emboli (12), and even cardiac arrest (13,14,19).

Research which has been performed using experimental animals gives wide support to these clinical findings (2). The first study on this subject was performed by Deichmann (5) in 1941. He administered oral methyl me tacrylate and observed the formation of gastric erosions, but no histopatological examination was performed. These experiments were performed using rabbits, quinea pigs, and rats, and he was able to calculate an oral LD_{50} of 8.41 ml/kg for rats.

In 1955 Spelman (16) and his colleagues investigated, for the first time, the effects of inhaling methyl metacrylate vapour. They were able to demonstrate a 50% mortality in rats breathing vapour at a concentration of 55 mg/lt for 3 hours.

According to a Soviet study (Dorofeeva, 1976) (6), MMA exposure caused above-normal incidence of headache, dizziness, loss of memory, and irritableness.

*From Hacettepe University, Faculty of Dentistry, Department of Prosthodontics.

** From Marmara University, Faculty of Medicine, Department of Pathology.

Tansy (17) and his associates commenced a series of experiments. Histopahological studies of the heart, kidney, spleen, stomach, small bowel, and adrenal tissue of rats which had inhaled 116 ppm methyl metacrylate vapour for 3 and 6 months, and of rats which had uniinterruptedly inhaled 1000 ppm methyl metacrylate vapour for 56 hours, showed no significant pathological changes.

In 1979 Innes, Tansy and Martin (11) let rats inhale methyl metacrylate vapour at a concentration of 400 ppm for a period of 60 minutes, and after a rest period of 30 minutes were able to demonstrate methyl metacrylate sensitive cells in the lateral hypothalamus and central hippocampal regions, using records taken from microelectrodes implanted stereotactically into their brains.

Christiansen and *et al.* (1986) (3) examined four patients who exposed for years to MMA using computed tomographic scanning, two of these were found to be normal and in to cases doubtful cortical atrophy was found. These investigations confirm the suspicion that MMA may produce acute and chronic CNS symptoms.

We have been unable to find any histopathological study of the effect of methyl metacrylate on brain tissues.

The frequent occurrence, amongst dental students and technicians, of disorders of the same type (such as gastritis, ulcerative stomach disease, phychic disorders, and pulmonary infections) characterized by similar symptoms, led us to determine the concentration of methyl metacrylate vapour in the air of our laboratory. Preliminary studies indicated that the concentration in the air of our laboratory was very low. Because of this and because in the literature generally the effects of high doses of methyl metacrylate have been investigated, we have chosen to study the effects of exposure to low doses of methyl metacrylate vapour.

The purpose of our research was to study the effect of low doses of methyl metacrylate on various organs. In this paper only the effects on the central nervous system will be discussed.

MATERIALS AND METHODS

Prior to exposing our subject animals to methyl metacrylate vapour it was first necessary to determine the daily dose and exposure time that we would use. The acryl flasking stage, at which point dental technicians are exposed to methyl metacrylate vapour was chosen as a criterion, and air was sampled during this process and analysed by gas chromatography. By this technique we determined the concentration of methyl metacrylate in the air as 0.45 ppm. Polyethylene glicol (PEG) in order to obtain a methyl metacrylate concentration of 0.45 ppm in the cages during the experiment 1 litre of was put in a 2 litre glass balloon and 2.25 ml of methyl metacrylate monomer (De Trey's) was added dropwise to it. Oxygen was passed through this mixture at a rate of 10 litres per minute vapoursing the methyl metacrylate and forming the desired concentration in the cage air.

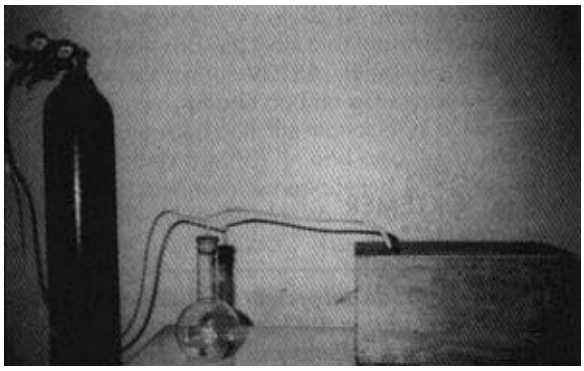

Figure 1: System used in the experiment.

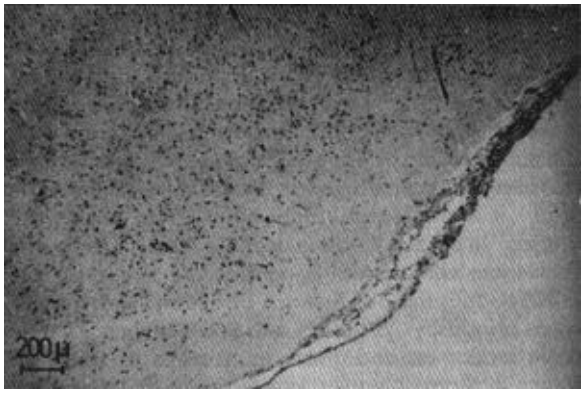

Figure 2: Leptomeningeal thickening and mononuclear cell infiltration in the 4 week test group.

Special wooden cages of dimensions 25x25x50 cm were used in these experiments. Two holes of egual diameter were made in the lid, through one of which methyl metacrylate and oxygen entered at a rate of 10 litres per minute whilst the carbon dioxide produced by the respiration of the animals exited at the same speed from the other (Figure 1).

This study was performed at the Medical and Surgical Research Centre of Hacettepe University using 60 male swiss albino rats weighting between 120 and 160 gr. Thirty rats were test animals and 30 were controls. Test groups composed of 10 rats were made to inhale methyl metacrylate vapour for 4, 8 or 12 weeks. Methyl metacrylate was administered 5 days per week for 1 hour each day. Control groups, each consisting of 10 animals were made to inhale pure oxygen passed through PEG under identifical conditions and for the same periods of times as the test animals.

At the end of the test period, the effect of methyl metacrylate vapour on the central nervous system was examined histopathologically.

Forty eight hours after the end of the test period rats were sacrificed. They were anaesthetized with nembutal (40 mg/kg) administered intraperitoneally. Following removal of the organs and blood,

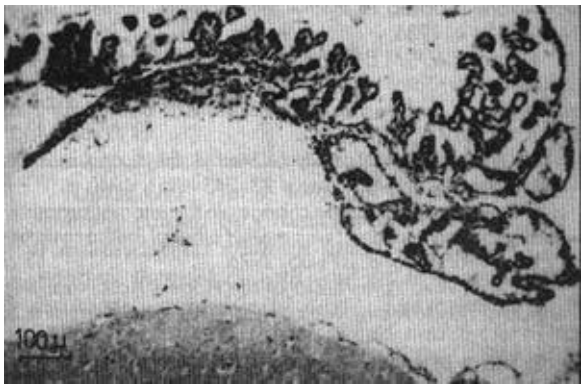

Figure 3: Plasma cells infiltration in the coroid plexus in the 4 week test group.

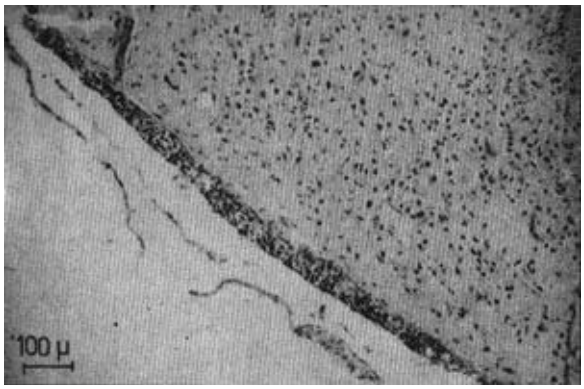

Figure 5: Control astrogliosis and linear mononuclear infiltration in the 8 week test group.

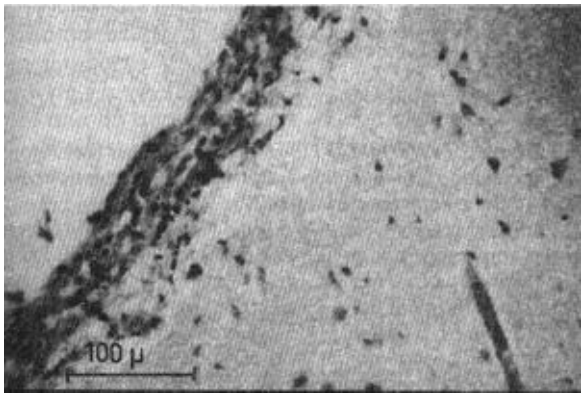

Figure 4: Leptomeningeal thickening and mononuclear cell infiltration in 8 week test group.

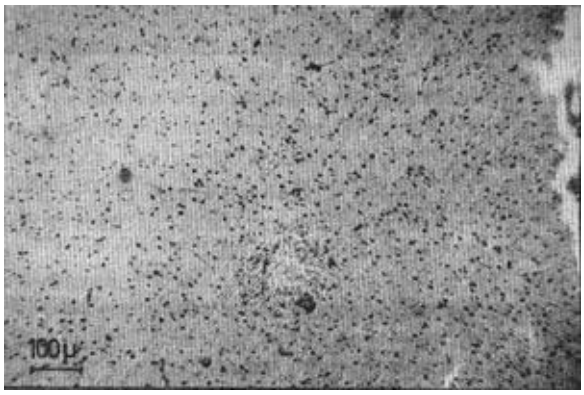

Figure 6: Facal tissue necrosis (microabscess) in the 8 week test groups.

the head was removed carefully from the neck, the brain was removed from the skull and fixed in 10% formalin for 2 weeks. After both hemispheres had been separated by saggital section, sections were prepared and stained with haemotoxylin eosin and examined under the light microscope.

RESULTS

Subject animals were divided into 3 groups and examined at 4, 8 and 12 weeks.

In the 4 week test group (group 1), in all animals varying grades of leptomeningeal thickening and mononuclear cell infiltration in this region were observed (Figure 2). These changes were not observed in the control group. In half of the animals in this group there was ependymal cell proliferation, oedema, and inflammatory cell infiltration in the subependymal area. In 3 cases mononuclear cell infiltration with plasma cells was observed in the choroid plexus (Figure 3). In 2 cases cellular infiltration of the same type occurred in the basal brain cortex.

In the 8 week group (group 2) leptomeningeal thickening and mononuclear cell infiltration was observed in all animals (Figure 4), and was more pronounced than that which occurred in the 4 week group. In half of the cases ependymitis and ventriculitis occurred, and in one case there was a local defect in the ependyma consisting of granulation tissue rich in blood vessels. In one third of cases there was cortical astrogliosis, and in an equal number of animals a dense linear mononuclear infiltration was observed directly beneath the leptomeninges (Figure 5). In one case perivascular mononuclear infiltration in the grey matter was observed to penetrate a pial vessel, whilst in the same case a dense mononuclear infiltration around the basal leptomeningeal vessel was observed. Again in one case focal tissue necrosis (a microabscess) was observed within the central nervous system (Figure 6), whilst in another instance a dense perivascular mononuclear infiltration in the central nervous system was seen.

In the 12 week group (Group 3) leptomeningeal thickening and mononuclear infiltration was observed in two thirds of the cases but was less pronounced than that observed in Group 2. Minimal inflammatory changes were observed in the intraventricular elements in 4 cases, and in 3 cases gliosis in the superficial cortex was observed (Figure 7). No pathological changes were found in the intracerebal tissue.

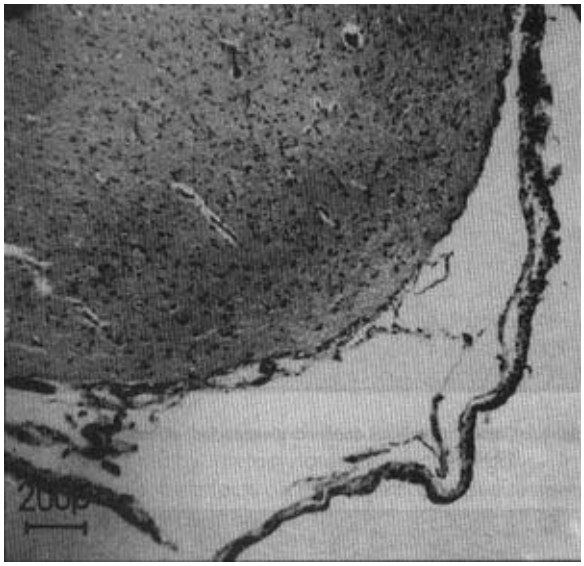

Figure 7: Gliosis in the superficial cortex in the 12 week test group.

DISCUSSION

As it is known, methyl metacrylate is a toxic substance. This substance has been shown to induce manifest histopathological changes in central nervous system tissue. These changes were most intense in rats exposed to the substance for 8 weeks, and found to be less in rats exposed to the substance for a shorter or longer period (Groups 1 and 3).

We postulate that the histopathological changes we have observed within the central nervous system have occurred due to the passage of toxic methyl metacrylate through the blood-brain barrier. The decrease of the intensity of findings at 12 weeks coupled with the occurrence of gliosis in this group suggests the existence of a reparative process.

The toxic substance disturbs the blood brain barrier, penetrates into the central nervous system, and induces harmful effects. The aetio-patnogenesis of the defect in the blood-brain barrier remains unclear.

The leptomeningeal thickening and cellular infiltration which we have observed in nearly all of our cases is probably due to chemical irritation (10).

The histopathological changes in the ependyma which were observed in half of our cases may be evidence of the penetration of the toxic substance (methyl metacrylate) into the central nervous system.

In areas in which methyl metacrylate is worked with, the ventilation systemic needs to be very good.

REFERENCES

1. Amstrutz HC: Complications of Total Hip Replacement Clin orthop 72:123, 1970.

2. Borzelleca JF, PS Larson, GR Hennigar Jr, EG Huf, EM Grawford, RB Smith Jr: Studies on the Chronic Oral Toxicity of Monomeric Ethyl Acrylate and Methyl Metacrylate. Toxicol, Appl Pharmacol 6:29, 1964.

3. Christiansen ML, et al: Is methylmetacrylate a cause of toxic brain damage? An investigation of a group of dental technicians exposed to methyl methacrylate. Ugeskr Laeger 148:1491-4, 1986.

4. Daniel WP, ME Converty, WE Miller: Pulmonary Complications after Total Hip Artroplasty With Charnley Prosthesis are Revealed by Chest Roentegenograms. J Bone Joint Surg 54-A:181, 1972.

5. Deichmann W: Toxicity of Methyl, Ethyl, and n-Butly Methacrylate. J Ind Hyg Toxical 23:243-351, 1941.

6. Dorofeeva ED: Some changes in the internal organs in workers coming in contact with methyl ether of methacrylic acid. Grig Tr Prof Zabol 8:31-35, 1976.

7. Fisher AA: Paresthesia of the Fingers accompanying Dermatitis Due to Methyl Methacrylate. Contact Dermatitis 5:56, 1979.

8. Fries LB, AA Fisher, EA Salvati: Contact Dermatitis in Surgeons From Methyl Metacrylate Bone Cement. J Bone Joint Surg 57-A:547, 1975.

9. Giunta J, N Zabotsky: Allerjik Stomatitis by Selfpolymerizing Resin. Oral Surg 41:631, 1976.

10. Greenhouse AH: The neuropathology of renal disease, in Minckler, J (ed): Pathology of the Nervous System. Vol. I New York, McGraw-Hill Book Co., pp 1029, 1968.

11. Innes DL, MF Tansy, JS Martin : Effects of Acute Methyl Methacrylate Inhalation on Rat Brain Neuronal Activity. J Dent Res 58:208, 1979.

12. Neal J, TI Wachtel, DT Graze, WS Edwards: Late Arterial Embolization Complicating Total Hip Replacement. A case report J Bone Joint Surg 61-A: 429, 1979.

13. Phillips H, PV Cole, AWF Lettin: Cardiovascular Effects of Implanted Acrylic Bone Cement. Brit Med 3:460-461, 1971.

14. Powell JN, PJ McGrawth, SK Lahiri, P Hill: Cardiac Arrest Associated With Bone Cement. Brit Med 3:326, 1970.

15. Schuh FT, ST Scluh, M kG Viguera, RN Terry: Circulatory Changes Following Implantation of Methyl Metacrylate Bone Cement. Anetsthesiology 39:455, 1973.

16. Spealman CR, RJ Main, HB Haag: Monomeric Methyl Methacrylate. Ind Med 14:292,298, 1945.

17. Tansy MF, FJ Hohenleitner, DK White, R Oberly, WE Landin, FM Kendall: Chronic Biological Effects of Methyl Methacrylate vapor III. Histopathology, Blood Chemistries and Hepatic and Ciliary Function in the Rat. Envir Res 21:117-215, 1980.

18. Turrell AJV: Allergy to Denture-base Materials-Fallacy or Reality. Brit Dental J 120:9, May 3, 1966.

19. Thomas TA, IC Sutherland, TD Waterhouse: Cold Curing Acrylic Bone Cement. A Clinical Study of the Cardiovascular Side Effects During Hip Joint Replacement. Anesthesia 26(3):298-299, 1971.