

Review Article

Mycophenolic acid: a drug with a potential beyond renal transplantation

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Received: 30 June 2016

Accepted: 29 July 2016

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ABSTRACT

Mycophenolic acid is an anti-metabolite immunosuppressant. It inhibits the enzyme inosine monophosphate dehydrogenase, which is essential for purine synthesis. It is indicated in prevention of rejection after renal transplantation. It is one of the few drugs, which were discovered more than a century ago and still in active use. This review discusses the other current and potential uses of the drug.

Keywords: Immunosuppressive agents, Kidney transplantation, Mycophenolic acid, Purines

INTRODUCTION

Mycophenolic acid (MPA) is an immunosuppressive drug used for the prevention of rejection in solid organ transplantation. MPA is not only effective in preventing rejection, being even superior to azathioprine, but also seems to cause less adverse effects than other immunosuppressive drugs.¹ It is one of the few drugs, which were discovered more than a century ago and still in active use. Because of favourable experiences with MPA in renal transplantation, the drug is currently used in patients with liver, lung and bone marrow transplantation as well.² MPA has also been used in renal, rheumatological, gastrointestinal, ophthalmological, dermatological and neurological autoimmune diseases.²

Mycophenolic acid (MPA) is a fungal metabolite that was initially discovered by Bartolomeo Gosio in 1893 as an antibiotic against anthrax bacillus, *Bacillus anthracis*.³ Because of its side effects profile and availability of safer antibiotics, MPA was and is not used as an antibiotic. But, studies continued on antibiotic action of MPA.⁴ Others studied actions of MPA in various other diseases. Though MPA remained out of clinical use for decades

after discovery in 1983, the interest of researchers in the molecule continued. Fortunately, the efforts of researchers were not futile. US FDA approved MPA in 1995 for prevention of rejection in renal transplant patients. Some studies reported MPA to also possess antiviral⁵ and antifungal activities.⁶ Some other studies reported antitumor, and antipsoriasis activities.^{7,8} So, it was found to be a broad-spectrum acting drug having antiviral, antifungal, antibacterial, anticancer, and antipsoriasis properties.⁹ In addition, MPA has anti-fibrotic effects.¹⁰

DETECTION OF IMMUNO SUPPRESSIVE ACTION

In the 1970s, Allison was looking into causes of immune deficiency diseases. He found that inosine monophosphate dehydrogenase (IMPDH), an enzyme, is causing undesirable immune response. He wanted to find a molecule that could suppress IMPDH. IMPDH is essential for the *de novo* synthesis of the purine guanine in lymphocytes. Lymphocytes do not have alternate pathway to synthesize guanine. Other human cells have alternate pathways to synthesize guanine. So a drug

blocking IMPDH will only affect lymphocytes and no other cells. By then mycophenolate mofetil was not in use as an antibiotic due to its side effects. In one of their experiments, Allison and his colleagues discovered that MPA blocks IMPDH. So purine synthesis is affected leading to inhibition of lymphocytes from proliferating. Hence they were able to prove that MPA has immunosuppressive activity.¹¹ Most other human cells use other pathways for synthesis of guanine and are therefore not or less affected by the anti-proliferative effect of MPA.

MECHANISM OF ACTION

MPA is a reversible inhibitor of IMPDH, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis.¹² Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA inhibits the proliferation of activated lymphocytes.

The depletion of guanosine nucleotides by MPA influences DNA synthesis and also glycosylation of adhesion molecules. Thereby MPA blocks proliferation and clonal expansion in T and B lymphocytes, inhibits antibody production and prevents the generation of cytotoxic T cells.

METABOLISM

Its empirical formula is $C_{17}H_{19}O_6Na$. The enteric-coated MPA tablet does not release MPA under acidic conditions ($pH < 5$) as in the stomach but is highly soluble in neutral pH conditions as in the intestine. To avoid the variability in MPA absorption between doses, MPA should be taken on an empty stomach. Mycophenolate mofetil is metabolised in the liver the active moiety mycophenolic acid.

MPA is metabolized principally by glucuronyl transferase to glucuronidated metabolites. MPA is conjugated in the liver into inactive mycophenolic acid glucuronide before being almost completely cleared by the kidney. Mycophenolate mofetil (MMF) is prodrug of MPA. Altered pharmacokinetics in patients with renal insufficiency might explain the increased rate of adverse effects, which can be managed by decreasing the dose of MMF.¹³ MPA is not substantially cleared by peritoneal or haemodialysis.¹³

USES OF MYCOPHENOLIC ACID

Mycophenolate is approved for use for the prevention of renal transplantation. But MPA has been tried in other conditions too. MPA offers an alternative treatment to patients who do not respond or are intolerant to current standard therapy. Its increasing application in lupus nephritis has shown more frequent complete response and less frequent complications compared to

cyclophosphamide bolus therapy.¹⁴ Walsh et al even propose that mycophenolate should be considered as a first-line induction therapy for treatment of lupus nephritis in patients without renal dysfunction.¹⁵

MPA has also been shown to be effective in patients with autoimmune diseases.¹⁶ MMF has also been studied in patients with autoimmune rheumatic diseases.¹⁷ It is also used for immunoglobulin A nephropathy, small vessel vasculitis and psoriasis.¹⁴ A study demonstrated activity of MPA against the novel MERS-CoV; its potent in vitro activity may allow it to be used as monotherapy.¹⁸ Mycophenolate mofetil is beginning to be used in the management of auto-immune disorders such as idiopathic thrombocytopenic purpura and systemic lupus erythematosus, scleroderma and pemphigus vulgaris with success for some patients.¹⁹ A combination of mycophenolate and ribavirin has been found to stop infection by and replication of dengue virus in vitro.²⁰

Information for patients

It is recommended that MPA be administered on an empty stomach, one hour before or two hours after food intake. In order to maintain the integrity of the enteric coating of the tablet, patients are instructed not to crush, chew, or cut MPA tablets and to swallow the tablets whole.

DOSAGE

The recommended dose of MPA is 720 mg administered twice daily on an empty stomach, one hour before or two hours after food intake. Patients with autoimmune disease who were switched from mycophenolate mofetil to enteric-coated mycophenolate sodium (EC-MPS) experienced less gastrointestinal symptom burden and showed improvement in general health-related quality of life (HRQoL).²¹

Conversion from MMF to EC-MPS was associated with a significant improvement in GI symptoms and HRQoL in liver transplant recipients.²²

Treatment during rejection episodes

Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of MPA is not required.

ADVERSE EFFECTS

Common adverse effects

Diarrhea, nausea, vomiting, joint pain, leucopenia, infections, anemia, fatigue and headache. Intravenous administration of mycophenolate mofetil is also commonly associated with local thrombosis.

Infrequent adverse effects

Though these are not common, but are a matter of concern. Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients.²³ GI hemorrhage, gastritis, esophagitis, pulmonary fibrosis, and lymphoma and other neoplasia have been reported. Pure red cell aplasia is also reported.²⁴

Occasional

The use of mycophenolate mofetil is known to be associated with progressive multifocal leukoencephalopathy (PML). Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. A Case of PML in a patient receiving MMF, who showed improvement upon discontinuation of the drug is reported.²⁵

Teratogenic

Pregnancy Category D

Biochemistry

Most common effect of this drug is increased blood lipid levels.

Drug interactions

Co-medication of pantoprazole with MMF significantly influences the drug exposure and immunosuppressive potency of MMF in patients with autoimmune diseases.²⁶

TREATMENT AND MANAGEMENT OF OVER DOSAGE

General supportive measures and symptomatic treatment should be followed in all cases of over dosage. Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA due to the 98% plasma protein binding of MPA. By interfering with enterohepatic circulation of MPA, activated charcoal or bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.

CONCLUSION

MPA is used to prevent rejection after transplantation. It may also be used in the treatment of many immunologically mediated diseases. In addition to the immune modulating effects, the anti-fibrotic and anti-proliferative effects of MPA can be especially valuable.

MPA may offer an alternative for cytotoxic alkylating drugs, in patients who cannot tolerate the latter. Immunosuppression may lead to increased susceptibility to

infection and possible development of lymphoma and other neoplasms.

Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should use mycophenolic acid.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Patro JP, Priyadarsini P. Mycophenolic acid: a drug with a potential beyond renal transplantation. *Int J Res Med Sci* 2016;4: 3666-9.