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Review Article

SAFETY PROFILE OF CYCLOSPORINE

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ABSTRACT

Background: Pharmacovigilance or drug safety is a pharmacological science related to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. Cyclosporine is approved by the FDA to prevent and treat graft-versus-host disease in bone-marrow transplantation and to prevent rejection of kidney, heart, and liver transplants. As beneficial effect of cyclosporine outweighs its adverse effects, yet it may cause severe adverse effects like kidney damage, convulsions, hypertension, liver damage, tremor, hirsutism, gingival hypertrophy, hyperkalaemia, fluid retention, increased susceptibility to infections, GI symptoms. Therefore, postmarketing surveillance of cyclosporine is necessary.

Objective: This paper examines safety data from the postmarketing surveillance studies of cyclosporine.

Methods: A search was performed to identify all studies published since 2004 concerning the safety profile of cyclosporine.

Conclusions: The study lead to the conclusion that all the adverse effects associated with cyclosporine are severe but no new adverse effect other than listed in the drug literature was found.

Keywords: Pharmacovigilance, Adverse effects, Immunosuppressants, Transplants, Postmarketing surveillance.

INTRODUCTION

Cyclosporine is an immunosuppressant drug widely used in organ transplantation to prevent rejection. It reduces the activity of the immune system by interfering with the activity and growth of T cells.[1,2] It was initially isolated from the fungus *Tolypocladium inflatum* (*Beauveria nivea*), found in a soil sample obtained in 1969 from Hardangervidda, Norway, by Hans Peter Frey, a Sandoz biologist.[3] Most peptides are synthesized by ribosomes, but cyclosporine is a cyclic nonribosomal peptide of 11 amino acids and contains a single D-amino acid, which are rarely encountered in nature.[4] The immunosuppressive effect of cyclosporine was discovered on 31 January 1972 by employees of Sandoz (now Novartis) in Basel, Switzerland, in a screening test on immune suppression designed and implemented by Hartmann F. Stähelin. The success of cyclosporine in preventing organ rejection was shown in kidney transplants by R.Y. Calne and colleagues at the University of Cambridge,[5] and in liver transplants performed by Thomas Starzl at the University of Pittsburgh Hospital. The first patient, on 9 March 1980, was a 28-year-old woman.[6] Cyclosporine was subsequently approved for use in 1983. Cyclosporine is approved by the FDA to prevent and treat graft-versus-host disease in bone-marrow

transplantation and to prevent rejection of kidney, heart, and liver transplants. It is also approved in the US for the treatment of rheumatoid arthritis and psoriasis and as an ophthalmic emulsion for the treatment of dry eyes.

Adverse drug effects may include kidney damage, convulsions, hypertension, liver damage, tremor, hirsutism, gingival hypertrophy, hyperkalaemia, fluid retention, increased susceptibility to infections, GI symptoms.[7] The most important effect of cyclosporine is to lower the activity of T cells and their immune response. Cyclosporine binds to the cytosolic protein cyclophilin (immunophilin) of lymphocytes, especially T cells. This complex of cyclosporine and cyclophilin inhibits calcineurin, which, under normal circumstances, is responsible for activating the transcription of interleukin 2. In T-cells, activation of the T-cell receptor normally increases intracellular calcium, which acts via calmodulin to activate calcineurin. Calcineurin then dephosphorylates the transcription factor nuclear factor of activated T-cells (NFATc), which moves to the nucleus of the T-cell and increases the activity of genes coding for IL-2 and related cytokines. Cyclosporine prevents the dephosphorylation of NF-AT by binding to cyclophilin.[8] It also inhibits lymphokine production and interleukin release and, therefore, leads to a reduced function of effector T-cells. It does not affect cytostatic activity.

Cyclosporine affects mitochondria by preventing the mitochondrial permeability transition pore from opening, thus inhibiting cytochrome c release, a potent apoptotic stimulation factor. It is a cyclic polypeptide containing 11 amino acids. It suppresses humoral immunity and to a great extent, cell mediated reactions. This action is due to a specific and reversible inhibition of immunocompetent lymphocytes in the G0 or G1 phases of cell cycle. T-helper cells are the main target but T-suppressor cells are also suppressed. It also inhibits lympholine production and release.

MATERIAL AND METHODS

A search was performed to identify all studies published since 2004 concerning the safety profiles of cyclosporine. More than 300 articles were identified that addressed safety issues, side-effect profiles, and tolerability concerns with the cyclosporine as an immunosuppressant agent. The data received was refined further to obtain useful information with the help of pre-programmed softwares and medical dictionary. Excel sheets were prepared and analysis was done using pivot table.

CONCLUSION

A line listing is prepared in the M S Excel spreadsheet. Using pivot tables, data is analysed based on time period, serious ADR, age group, gender and country of incidence. The data obtained in the form of tables resulted in the evolution of the conclusion that all the ADRs which come to the fore are already mentioned in the drug literature and no substantial ADR is reported. Hence, cyclosporine met the safety parameters.

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