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Comparative pre-clinical and clinical experience with oral polio vaccine produced on MRC-5 cells or on primary monkey kidney cells

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Abstract

The need to avoid using primates has prompted the replacement of primary monkey kidney cells (PMKC) as a substrate for oral polio vaccine (OPV) production. Here, we report on OPV produced on MRC-5 cells using an industrial process capable of producing over 1 billion doses. All serotypes produced on MRC-5 cells proved satisfactory in the monkey and transgenic mice neurovirulence tests. All the type 3 MRC-5 lots tested by Mutant Analysis by PCR and Restriction Enzyme Cleavage (MAPREC) had a 472-C content below the acceptable limit and similar to that of PMKC derived lots. The safety/reactogenicity and immunogenicity profiles following vaccination in infants and children were similar for OPV MRC-5 and OPV PMKC vaccine lots. Excretion rates and prevalence of revertants for the three serotypes following vaccination were also similar for both vaccines. These data support the use of MRC-5 cells as an alternative to PMKC for OPV production.
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1. Introduction

The availability of large quantities of MRC-5 cells derived oral polio vaccine (OPV) now provides a replacement for vaccine produced on primary monkey kidney cells (PMKC). The trivalent Sabin live attenuated OPV containing type 1, 2 and 3 viruses has been used for more than 30 years to successfully control paralytic polio. Its impressive safety and efficacy profile together with the low cost of production and ease of administration has made OPV the major tool in the global poliomyelitis eradication programme. Billions of doses have been used in World Health Organization (WHO) mass vaccination programmes.

OPV has traditionally been produced by the propagation of the three poliovirus strains on primary monkey kidney cell cultures. Candidate donor monkeys require careful quarantine and screening before use. It is, however, becoming increasingly difficult to obtain healthy animals that meet these stringent requirements. There is also increased pressure from public opinion to reduce or avoid the use of animals, especially primates in commercial production due to industrialisation of the MRC-5 cell culture process. A key breakthrough in the availability of a new test for neurovirulence, which avoids the use of monkeys for quality control purposes, has also prompted a shift of OPV production away from the use of monkeys.

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The obvious candidates for replacement of PMKC are established and well-characterised cell lines such as MRC-5 or Vero cells [1]. GlaxoSmithKline (GSK) Biologicals, which has been involved in the manufacture of OPV since the early 60's and is one of the main producers, has developed a vaccine produced on the MRC-5 cell line. This human diploid line, established in the 1960s, has been widely used for the large scale commercial production of other vaccines such as hepatitis A, rubella and varicella and was used in the UK in the 1960's to produce limited quantities of OPV.

The polio Sabin strains are known to be relatively unstable and their attenuation status can be altered during passage in cell culture. This means that polio vaccines have to be manufactured under strictly controlled conditions and to undergo rigourous biological testing. The susceptibility to deattenuation can be influenced by several factors including the cell substrate used [2]. It was essential, therefore, to establish for each of the three serotypes, that the change in cell substrate did not alter the genetic stability, the potential for neurovirulence, the consistency of production or the clinical profile. This report describes the pre-clinical and clinical characteristics of OPV produced on MRC-5 cells (OPV MRC-5) relative to the traditional GSK OPV produced on PMKC cells (OPV PMKC) using a process which allows production of over one billion doses per year.

During in vitro propagation of the three OPV serotypes in cell culture, reversions to wild type occur in the 5′-untranslated RNA regions. Key mutations have been identified which are related to the expression of neurovirulence, the basis of poliovirus pathogenicity in humans. These involve a change from G to A at position 480 for type 1 [3,4], a change from A to G [5,6] at position 481 for type 2 and a change from U to C [7,8,9] at position 472 for type 3. Each manufactured monovalent vaccine bulk has therefore to be tested for stability of attenuation by the in vivo monkey neurovirulence test before use in humans. Recently, an alternative in vivo neurovirulence test has been developed which involves the use of transgenic TgPVR21 mice instead of monkeys [10]. Unlike normal mice, the transgenic mice are susceptible to poliovirus infection and the clinical pathology closely resembles that found in primates. A very sensitive in vitro procedure, Mutant Analysis by PCR and Restriction Enzyme Cleavage (MAPREC), has also been developed to quantify reversion of the key point mutations linked to neurovirulence [11]. Both in vivo neurovirulence tests and MAPREC were used to assess the genetic stability of OPV MRC-5 with respect to OPV PMKC.

Selection of revertant poliovirus strains also occurs during propagation in vivo in the gastrointestinal tract following vaccination [12,13,14]. The genetic stability of OPV MRC-5 in vivo was therefore assessed relative to OPV PMKC in a clinical study where the excretion rates of the three poliovirus strains and the prevalence of revertants were monitored in the stools of vaccinated infants.

2. Methods

2.1. Vaccines

The production of the monovalent vaccine bulks was based on the seed lot principle and followed the recommendations of the European Pharmacopoeia (Ph. Eur.) and WHO with regard to temperature for virus propagation and time of harvest. Each of the three poliovirus seed lots (prepared on PMKC) was propagated on either MRC-5 cells or PMKC cells. All vaccine bulk lots were manufactured at passage level SO+3 (SO: Sabin original) for types 1 and 2 and RSO3 (RSO: RNA-derived Sabin original) for type 3 viruses. All bulks were tested according to WHO requirements in force at the time of their production [15,16]. The trivalent final OPV vaccines were formulated and tested in compliance with WHO and Ph. Eur. requirements with each vaccine containing not less than $10^{6.0}$ $CCID_{50}$ type 1, $10^{5.0}$ $CCID_{50}$ type 2 and $10^{5.8}$ ($10^{5.5}$ for Ph. Eur.) $CCID_{50}$ type 3 polioviruses.

2.2. Monkey neurovirulence test

OPV monovalent bulks of each of the three serotypes derived from production on MRC-5 were tested in comparison with PMKC derived bulks for neurovirulence in monkeys as described by WHO [15,17].

2.3. Transgenic mice neurovirulence test

Testing for neurovirulence in transgenic mice for type 3 poliovirus was performed as described by WHO [15,17]. More recently, WHO has also recommended the transgenic mice test for types 1 and 2 [18].

2.4. MAPREC

The MAPREC test was performed on MRC-5 and PMKC derived OPV type 3 bulks as described in the WHO standard operating procedure [19]. Data are expressed as a ratio of the 472-C content of an international reference. A lot passes the test if the ratio is below 1.

2.5. Clinical studies

One open booster vaccination study in healthy children and three double blind randomized primary vaccination studies in healthy infants were performed with OPV MRC-5 as summarised in Table 1. The design and implementation of each trial took into account the Good Clinical Practice Guidelines in use at the time of the initiation of the study. All study protocols underwent Ethics Review Board appraisal. Studies were performed in accordance with the Declaration of Helsinki and its amendments. Informed consent was obtained from the parents/guardians of all infants before enrolment in the studies.

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