ABSTRACT

Patients' preference concerning fixed dose combination as anti tuberculosis drug in accordance with DOTS program

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Tuberculosis always requires a multi-drug therapy. A good quality of fixed dose combination (FDC) will ensure dose delivery accurately, and may thereby facilitate to prevent anti tuberculosis drug resistance when is given in sequence with directly observed treatment short-course (DOTS) program guidelines. The fewer drugs to consume daily, the better acceptance of the society toward presentation form and taste will create a TB treatment easier. For this reason a three step studies has been conducted to prepare a good quality formulation of fixed dose combination in accordance with DOTS that is suitable for TB patients.

The first step of the study was to recognize the best form and taste that will be well accepted by TB patients. The questionnaire was utilized for 100 of TB patients, who discontinued the treatment before 6 months period (drop out), along with 50 patients who could continue the treatment standard for 6 months period. The objective of this study was to investigate the reasons of treatment discontinuation, and to discover the best form and taste of TB drugs.

The second step was to prepare FDC with a good formulation that fits the need of TB patients. The objective were to prepare a good stability and taste of FDC. The equipments used were UV-VIS spectrophotometer, FT/IR spectrophotometer and climatic chamber.

The third step was treatment by subject. As a preliminary study, 9 healthy volunteers took FDC and 8 single-drugs in accordance with DOTS (Kombipak II), as a cross over study design, with 3 days of washing out period. Consequently 9 of healthy volunteers took FDC formulation and Kombipak II, in another cross over study design with 7 days of washing out period. The objective was to compare bioavailability profile of FDC and Kombipak II. The equipment used in this study was UV-VIS spectrophotometer.

The result of the first study showed the patients' preference to a good flavor (not a bitter taste) were 69% discontinue treatment group and 72% continue treatment group and the patients' preference to dry syrup sachet were 82% discontinue treatment group and 62% continue treatment group.

The second study showed that FDC of isoniazid-ethambutol-pyrazinamide was stable in the condition of 30°C and 40°C, however was being unstable in the condition of 70°C for 14 days period. Since mass TB eradication program should be cheap, consequently rifampicin has to be separated in small sachet together with each sachet of FDC.

The third study showed that in comparison with Kombipak II, FDCs dry syrup was the same profile in term of maximal plasma concentration Cp max, maximal concentration time T max, and area under curve (AUC).

The conclusion was a three step study had been conducted successfully for preparing fixed dose combination in accordance with DOTS, in a good quality sachet form that appropriate with the need of TB patients.

A further study is suggested to search for the best formulation and clinical trials.

Key words : Fixed-dose combinations, DOTS, stability, bioavailability, AUC

RINGKASAN

SEDIAAN TUNGGAL
OBAT ANTI TUBERKULOSIS PROGRAM DOTS
BERBASIS PILIHAN PENDERITA

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Sampai saat ini tuberkulosis belum berhasil diberantas, bahkan semakin sulit dengan berkembangnya kuman kebal kombinasi obat dan banyaknya penderita HIV/AIDS yang tertular tuberkulosis, walaupun sudah ada obat yang efektif membunuh kuman tuberkulosis terdiri atas kombinasi 4 macam obat dan memerlukan waktu minimal 6 bulan. Salah satu sebab kegagalan program pemberantasan tuberkulosis adalah tingginya angka putus berobat. Kendalanya adalah harus minum banyak tablet yang sebagiannya pahit selama minimal 6 bulan walaupun gratis. Salah satu cara untuk mengatasi hal tersebut adalah dengan menyediakan obat sederhana yang paling diterima penderita.

Tujuan dari penelitian ini adalah untuk mendapatkan sediaan obat anti tuberkulosis program *Directly Observe Treatment Shortcourse* (DOTS) dalam satu sediaan kombinasi tetap (*fixed-dose combination*) dalam bentuk dan rasa yang paling diterima oleh penderita tuberkulosis, dan tertanggung jawab secara farmasi.

Untuk mencapai tujuan tersebut dilakukan penelitian 3 tahap:

1. Mengetahui sebab putus berobat, menetapkan bentuk dan rasa obat yang paling diterima penderita. Dengan cara menyiapkan kuesioner untuk 100 penderita putus berobat dan 50 penderita yang taat berobat selama minimal 6 bulan. Hasil penelitian pertama menunjukkan bahwa masalah obat merupakan salah satu sebab dari putus berobat (62% responden taat berobat dan 74% penderita

putus berobat), sedang bentuk obat yang paling diterima adalah sirup kering dalam bungkus perdosis (62% responden taat berobat dan 82% penderita putus berobat) dengan rasa asal tidak pahit (72% responden taat berobat dan 69% penderita putus berobat).

2. Mempersiapkan Sediaan Tunggal Obat Anti Tuberkulosis (SOT). merupakan obat kombinasi dosis tetap, sesuai program DOTS. sesuai dengan bentuk dan rasa yang paling diterima penderita. Oleh karena World Health Organization (WHO) dan International Union Against Tuberculosis and Lung Diseases (IUATLD) menyatakan bahwa pencampuran rifampisin dengan obat anti tuberkulosis lain memerlukan kontrol bioekivalensi berkala dan mahal sehingga membuat sediaan jadi mahal, maka rifampisin dipisah tersendiri supaya SOT tidak mahal dan rumit untuk program pemberantasan tuberkulosis. Dilakukan penelitian stabiliti untuk campuran isoniazid. etambutol dan pirazinamid. Alat yang dipakai pada penelitian ini adalah spektrofotometer UV-Vis HP-8452A, spektrofotometer Jasco FT/IR-5300 dan climatic chamber Climacell MMM 111. Stabiliti diteliti dengan metode *accelerated stability test* pada suhu 30°C,40°C, dan 70°C. Dari penelitian kedua ini telah dibuktikan bahwa campuran isoniazid, etambutol dan pirazinamid stabil pada suhu 30°C dan 40°C, tetapi tidak stabil pada penyimpanan suhu 70 °C selama 14 hari. Namun pirazinamid tunggal juga tidak stabil pada penyimpanan suhu 70°C selama 14 hari.

3. Penelitian bertujuan membandingkan bioavailabiliti 8 tablet obat anti tuberkulosis program DOTS (Kombipak II) dan 1 saset SOT

(*crossover experimental study*). Dilakukan studi awal terhadap 9 orang sehat masing-masing menelan 8 tablet Kombipak II dan 1 bungkus campuran SOT dengan selang waktu. Dilanjutkan dengan 3 orang sehat masing masing menelan 8 tablet Kombipak II dan 1 formulasi SOT dengan selang waktu *wash-out* 7 hari. Diukur kadar bahan obat dalam darah berturut-turut mulai 0 sampai 8 jam. Dengan memakai spektrofotometer UV-Vis. Penelitian ketiga menunjukkan bahwa formulasi SOT mempunyai keunggulan tak berbeda dibanding Kombipak II dalam masalah: Konsentrasi maksimal dalam darah (Cp maks), kecepatan mencapai konsentrasi maksimal (T maks), dan area di bawah kurva (*area under curve, AUC*).

Kesimpulan dari penelitian-penelitian ini menunjukkan bahwa: Faktor obat merupakan salah satu sebab putus berobat. Sediaan yang paling diterima penderita adalah sediaan tunggal obat anti tuberkulosis (SOT), merupakan kombinasi dosis tetap berupa sirup kering dalam saset perdosis terdiri dari isoniazid, etambutol, pirazinamid dan rifampisin. Secara farmasi SOT setara dibanding 8 tablet Kombipak II.

Disarankan untuk segera melakukan penyempurnaan formulasi, uji stabiliti dan bioavailabiliti lebih lanjut, disusul dengan uji klinik, untuk kemudian didaftarkan sebagai hak paten. Dalam bentuk sirup kering dengan rasa tidak pahit, dengan penyesuaian dosis bisa diharapkan menjadi obat pilihan utama pada anak. Dengan pola yang serupa bisa diterapkan untuk pengobatan penyakit yang kronis dan memerlukan obat kombinasi.

SUMMARY

Patients' preference concerning fixed dose combination as anti tuberculosis drug in accordance with DOTS program

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The idea of using Fixed-dose combination (FDC) for the treatment of tuberculosis arose from the fact that tuberculosis always requires multi-drug therapy. Fixed-dose combination of good quality ensure accurate dose delivery, and may thereby help to prevent anti TB drug-resistance when given as directly observed treatment as recommended in the DOTS strategy. When using single-drug formulations, patients are more prone to interrupt their treatment on some drugs while not on others, thereby creating a risk of mono-therapy and selection of drug-resistant mutants.

Many patients complain about size, quantity to be ingested or difficulty with swallowing and taste of drugs. Fewer drugs to swallow per day, social acceptance to drugs form and taste no doubt will make treatment easier. For this reason a three-step study has been conducted to prepare fixed-dose combination in DOTS strategy, in one good quality formulation that suitable for tuberculosis patients.

The first step of the study was to know the best form and taste that will accept by tuberculosis patients, using questionnaire, was taken from 100 tuberculosis patients that stop treatment before 6 months (drop-out), and 50 tuberculosis patients that continuous treatment for 6 months. Objective of this study was to know the cause to early stop treatment, the best form and taste of the TB drugs.

The second step of the study was to prepare fixed-dose combination in DOTS strategy, in good formulation that suitable for tuberculosis patients. Objectives of this study were to prepare isoniazid, ethambutol and pirazinamide in one sachet, with good stability and quality, and good taste. WHO and IUATLD stated that bioequivalence of rifampicin containing FDC must be established, this is an expensive process. Because mass tuberculosis eradication program must be cheap, so in this study rifampicin separated in small sachet including in the every FDC sachet. The equipments used in this study were Spectrophotometer UV-Vis HP-8452A, Spectrophotometer Jasco FT/IR-5300 and Climatic chamber Climacell MMM 111.

The third step of the study was treatment by subject, as pre-clinical experimental study. 3 healthy volunteer taken both kinds of drugs (FDC alluminium sachet and 8 single-drugs DOTS) as crossover design, at 7 days washing-out periode. The objective of this study was to compare bioavailability in vivo of FDC alluminium sachet with 8 single-drugs DOTS (Kombipak II). The equipment used in this study was spectrophotometer UV-Vis.

The results of the first study showed that a not bitter taste (69% drop out respondents and 72% compliance respondents), dry-syrup in one sachet per dose (82% drop out respondents and 62% compliance respondents) were the patients choice.

The result of the second study showed that FDC isoniacide-pirazinamide-ethambutol stable in 30 C and 40 C, but unstable in 70 C for 14 days.

The results of the third study showed that in comparison with Kombipa II tablets, FDC dry-syrup similar in: maximal plasma concentration Cp.max, maximal concentration time T max. area under curve AUC.

The conclusion was a three-step study has been conducted successfully to prepared fixed-dose combination in DOTS strategy, in one aluminium sachet good quality formulation, that suitable for tuberculosis patients.

The next studies will be clinical trial (local, national multicentre, international multicentre) and studies for the best formulation to be patented.