(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 January 2003 (16.01.2003)

PCT

(10) International Publication Number
WO 03/004079 A1

(51) International Patent Classification[7]: A61M 5/145

(21) International Application Number: PCT/GB02/02932

(22) International Filing Date: 26 June 2002 (26.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0116076.1 2 July 2001 (02.07.2001) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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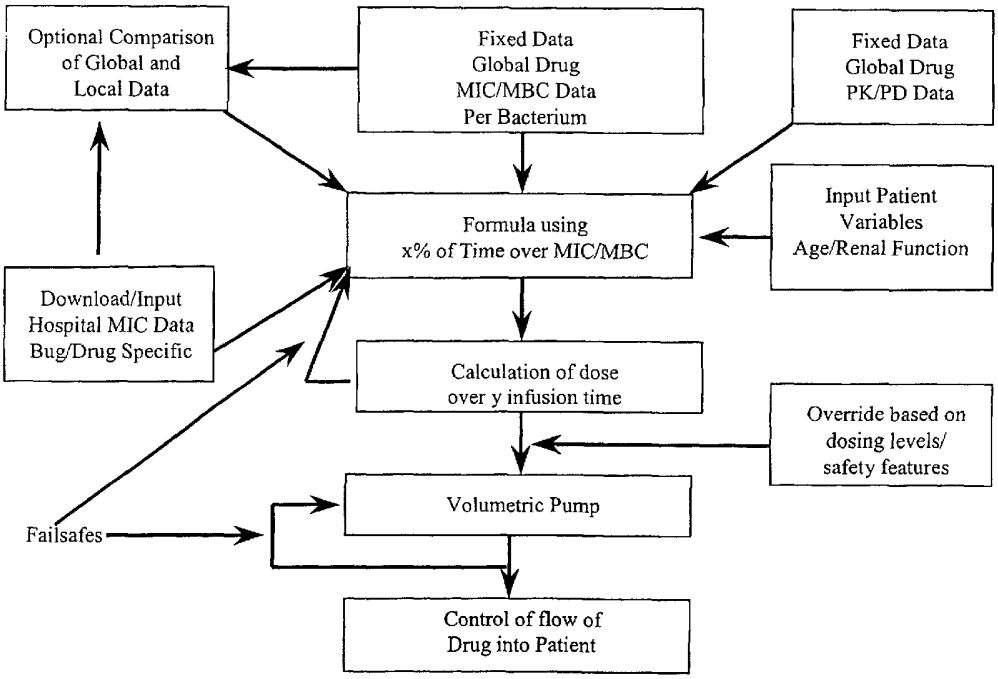
(54) Title: ANTIBIOTIC DRUG DELIVERY SYSTEM



(57) Abstract: An antibiotic drug delivery system for controlled infusion of an antibiotic drug to a patient, which system comprises (i) a delivery device for providing an infusion of the antibiotic at a controlled rate, together with (ii) a control system for varying the infusion rate and time of dosing of the antibiotic according to one or more parameters of the drug so as to maintain antibiotic levels in the patient of a desired percentage above the accepted MBC or MPC for that antibiotic.

WO 03/004079 A1

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANTIBIOTIC DRUG DELIVERY SYSTEM

The invention relates to the field of antibacterial agents. In particular it relates to improvements in infusion of antibiotic drugs and an apparatus for providing controlled infusion of such drugs.

The dosing of antibiotics is historically based on three factors:-

a) The drugs half life dictating once every 24hrs (q24); every 12 hours (q12); every 8 hours (q8) or every 6 hours (q6).

b) The dose selected, chosen by using the Minimum Inhibitory Concentration (MIC) for the range of bacteria the antibiotic is effective against and then taking the 'breakpoint' MIC for the majority of organisms and dosing to achieve this concentration level.

c) Tolerability at the various dosing levels is taken into account.

Since the majority of antibiotics gained regulatory approval, several authors have confirmed that pharmacokinetically the correct dosing targets for several classes of antibiotics are to achieve drug levels above the MIC for a certain percentage of the dosing interval. This percentage value is variable for different drug classes e.g. carbapenems are 40% and penicillins and cephalosporins are between 50% and 60% of the time. This rule is seen as being general for that class of drug and has been illustrated by several workers including Vogelman B et al. J Infect Dis 1988; 158:831-847; Am J Med 77 (suppl 6A):43; R. Walker, D. Andes, R. Conklin, S.Ebert W. Craig; Clin Infec Dis 1998; Craig WA et al

It is generally accepted that a dead bug cannot mutate and pass on resistance. The two measures of this are MBC as in the Maximal Concentration required to kill the Bacterium and MPC which is the Mutant Prevention Concentration (cf. Tulkins, Mouton ISAP Conference at ECCMID, April 2001). The MPC may be seen as an antibiotic concentration that will quickly kill all bacteria and kill bacteria with decreased susceptibility.

Additional work has shown that improved results over normal dosing methods can be achieved by using longer infusions instead of intermittent dosing. Thus 1-3 hour infusions,

instead of bolus dosing or infusions under 30 minutes, may achieve better microbiological results, dependent upon the bacterium and antibacterial.

At present, delivery of antibiotics at the bedside is often via an infusion bag dripped into a patient over a 30 minute time period or via bolus injection from a syringe over a shorter time period. Thus the whole process does not take account of the pharmacokinetic principle and may result in overdosing to ensure efficacy. That is to say if one dose is applied to all MIC's, it may result in overdosing for some organisms and under dosing for others.

In summary, current methods for delivering continuous infusions may result for example in tolerance problems, overdosing, underdosing, and the development of antibiotic resistance.

The invention is based at least in part on the realisation that pharmacokinetic data for a particular antibiotic drug can be used to derive infusion characteristics for that drug which can be programmed into a delivery system to provide controlled infusion of that particular drug. We believe that a delivery system that uses such infusion characteristics may be able to provide the best available administration regime for that particular drug. We anticipate that use of the system will mean less antibiotic is required per therapeutic treatment and that treatment times will be shorter.

Specifically, such a system allows dosing for optimal resolution of the infection, by controlling the dosing levels of the antibacterial to prevent the bacterium from passing on resistance to other bacteria.

Therefore in a first aspect of the present invention we provide an antibiotic drug delivery system for controlled infusion of an antibiotic drug to a patient, which system comprises

(i) a delivery device for providing an infusion of the antibiotic at a controlled rate, together with

(ii) a control system for varying the infusion rate and time of dosing of the antibiotic according to one or more parameters of the drug so as to maintain antibiotic levels

in the patient of a desired percentage above the accepted MBC or MPC for that antibiotic.

The parameters of the drug include, without limitation, pharmacokinetic and pharmacodynamic parameters and the derived MBC or MPC concentrations. The MBC or MPC concentrations are either calculated or measured.

It will be understood that the delivery device for providing a continuous infusion of the antibiotic include conventional devices such as pumps, syringes, control valves. In general terms, the antibiotic drug is kept in a reservoir such as a bag, vial or syringe and then pumped or gravity fed. Often the device will comprise two main elements such as for example a reservoir and pump or a syringe and mechanical means acting on the syringe plunger and/or barrel.

Particularly useful devices include pumps used for target controlled infusion in other technical fields such as the Diprifusor™ pump used for delivering the anaesthetic Diprivan (propofol). See for example US patent numbers 5882338 and 6019745, also PCT/GB94/00909.

The control system for varying the infusion rate of the antibiotic according to one or more pharmacokinetic parameters so as to maintain antibiotic levels in the patient of a desired percentage above the MBC or MPC for that antibiotic, may comprise any mechanical and/or electrical elements. The relevant instructions for the control system may for example be provided via an optical recognition system eg. barcodes/scanner or radiofrequency devices. In particular aspects of the invention the instructions are conveniently provided on any convenient data storage medium. Without limitation this may be a computer (such as a PC) or a computer chip holding the relevant mechanistic data eg. pharmacokinetic formula and MIC data for a given antibiotic/bacterium combination

The control system for varying the infusion rate and time of dosing of the antibiotic according to one or more of its mechanistic parameters so as to maintain antibiotic levels in the patient of a desired percentage above the accepted MIC for that antibiotic represents a further and independent aspect of the invention.

The control system is conveniently programmed to reflect globally available mechanistic parameters and/or patient data for a given drug. This may be supplemented by local hospital data and/or local patient data. If desired, one or more of these may be entered manually at any time prior to treatment. By way of non-limiting example patient age, weight, renal status and other personal information may be entered immediately prior to treatment.

The control system may be set up to compare global and local data and to act accordingly. If required a manual override facility may be provided. It will be appreciated that such a facility must be used with caution.

In a further aspect of the invention the control system is provided with one or more failsafes. These can be used for example to ensure that proscribed maximum and minimum values are not exceeded and cannot be overridden.

Any convenient percentage (calculated or measured) about the MBC or MPC may be selected if appropriate for a given microorganism. Whilst we don't wish to be limited by theoretical considerations this could be up to 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100% above the MIC. Still further it could be more than 100%.

The drug delivery system of the invention may be used to deliver any convenient antibiotic drug. These include all carbapenems such as meropenem, imipenem, imipenem/cilastatin, ertapenem, banipenem, and in particular meropenem. Further antibiotics include penems such as faropenem; cephalosporins such as ceftriaxone, cefepime, and ceftazidime; penicillins such as ampicillin; oxazolidinones such as linezolid. The system may also be used to deliver drug combinations such as piperacillin/tazobactam.

A further aspect of the invention relates to the use of the drug delivery system of the invention for the infusion of an antibiotic drug.

Another aspect of the invention relates to a method of treatment of the human or animal body using an antibiotic drug which method comprises the use of the drug delivery system of the invention.

The drug delivery system of the invention may be used to provide antibiotic treatment for all hospital in-patient and out-patient therapy indications.

The patient may be human or animal.

The invention will now be illustrated, but not limited, by reference to the following Figures wherein:

Figure 1 shows current dosing stragegy and the likely antibiotic concentration in a patient measured against time in comparison with the MIC of an average bacterium.

Figure 2 shows the controlled antibiotic dose above the MIC and MBC or MPC of a specific bacterium as may be established in a patient using the drug delivery system of the invention.

Figure 3 illustrates elements of a control system for varying the infusion rate and time of dosing.

CLAIMS

1. An antibiotic drug delivery system for controlled infusion of an antibiotic drug to a patient, which system comprises

(i) a delivery device for providing an infusion of the antibiotic at a controlled rate, together with

(ii) a control system for varying the infusion rate and time of dosing of the antibiotic according to one or more parameters of the drug so as to maintain antibiotic levels in the patient of a desired percentage above the accepted MBC or MPC for that antibiotic.

2. An antibiotic drug delivery system as claimed in claim 1 and wherein the delivery device comprises a reservoir and pump.

3. An antibiotic drug delivery system as claimed in claim 1 and wherein the delivery device comprises a syringe and mechanical means acting on the syringe plunger and/or barrel.

4. An antibiotic drug delivery system as claimed in claim 1 and wherein the control system includes instructions provided on a data storage medium.

5. An antibiotic drug delivery system as claimed in claim 4 and wherein the data storage medium is a computer chip

6. An antibiotic drug delivery system as claimed in claim 4 and wherein the data storage medium is a computer.

7. An antibiotic drug delivery system as claimed in any preceeding claim and wherein the control system includes mechanistic data for one or more antibiotic/bacterium combinations.

8. An antibiotic drug delivery system as claimed in any preceeding claim and wherein the control system includes local mechanistic and/or patient data for one or more antibiotic/bacterium combinations.

9. An antibiotic drug delivery system as claimed in any preceeding claim and wherein the control system includes global mechanistic and/or patient data for one or more antibiotic/bacterium combinations.

10. An antibiotic drug delivery system as claimed in claim 1 and wherein the control system is set up to compare local and global mechanistic and/or patient data for one or more antibiotic/bacterium combinations.

11. An antibiotic drug delivery system as claimed in claim 1 and further comprising a manual override facility.

12. An antibiotic drug delivery system as claimed in claim 1 and further comprising one or more failsafes.

13. A computer chip comprising instructions system for varying the infusion rate and time of dosing of an antibiotic according to one or more parameters of the drug so as to maintain antibiotic levels in a patient of a desired percentage above the accepted MBC or MPC for that antibiotic.

14. A control system for varying the infusion rate and time of dosing of an antibiotic according to one or more parameters of the drug so as to maintain antibiotic levels in a patient of a desired percentage above the accepted MBC or MPC for that antibiotic.

15. Use of an antibiotic drug delivery system as claimed in claim 1 for controlled infusion of a carbapenem antibiotic.

16. Use of an antibiotic drug delivery system as claimed in claim 1 for controlled infusion of a penem antibiotic.

17. Use of an antibiotic drug delivery system as claimed in claim 1 for controlled infusion of an oxazolidinone antibiotic.

Figure 1

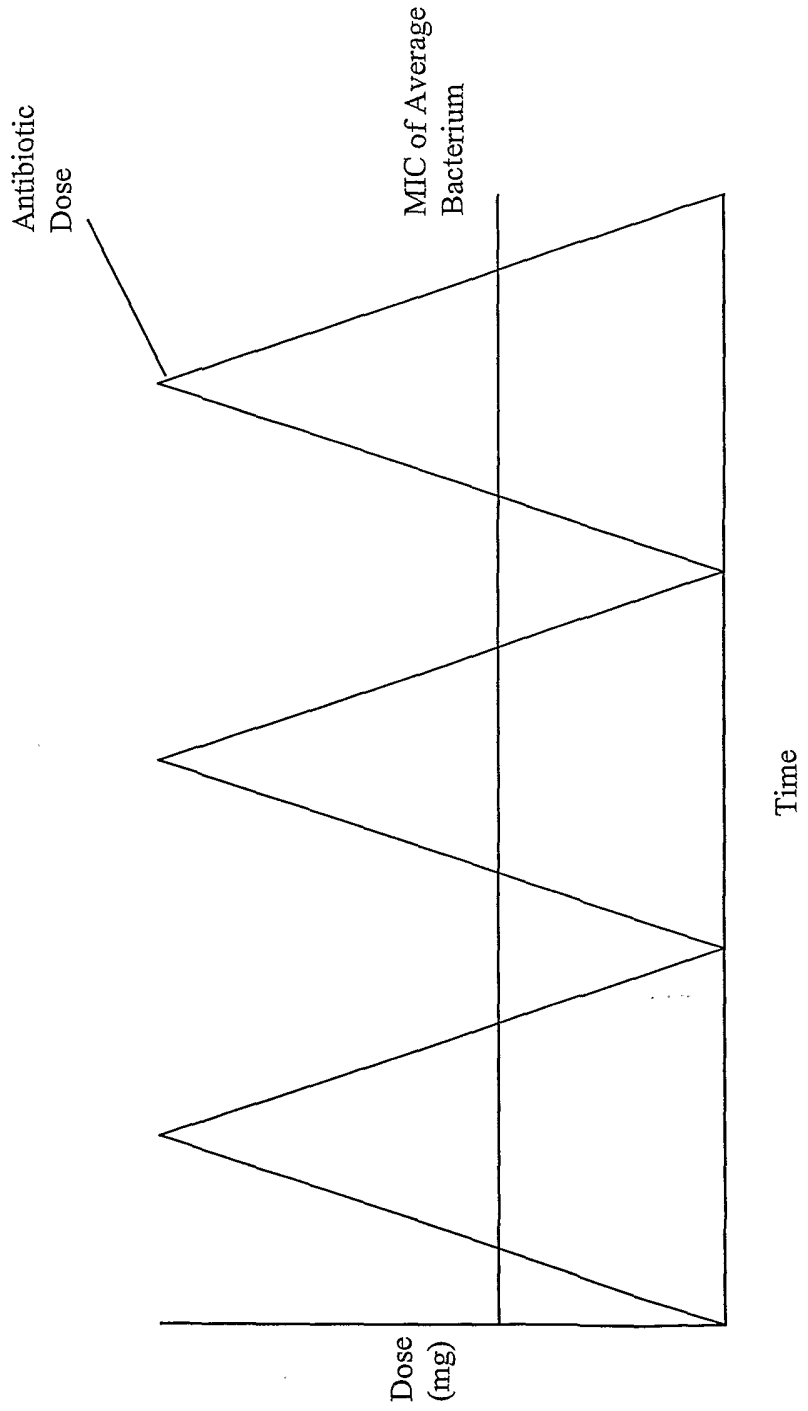


Figure 2

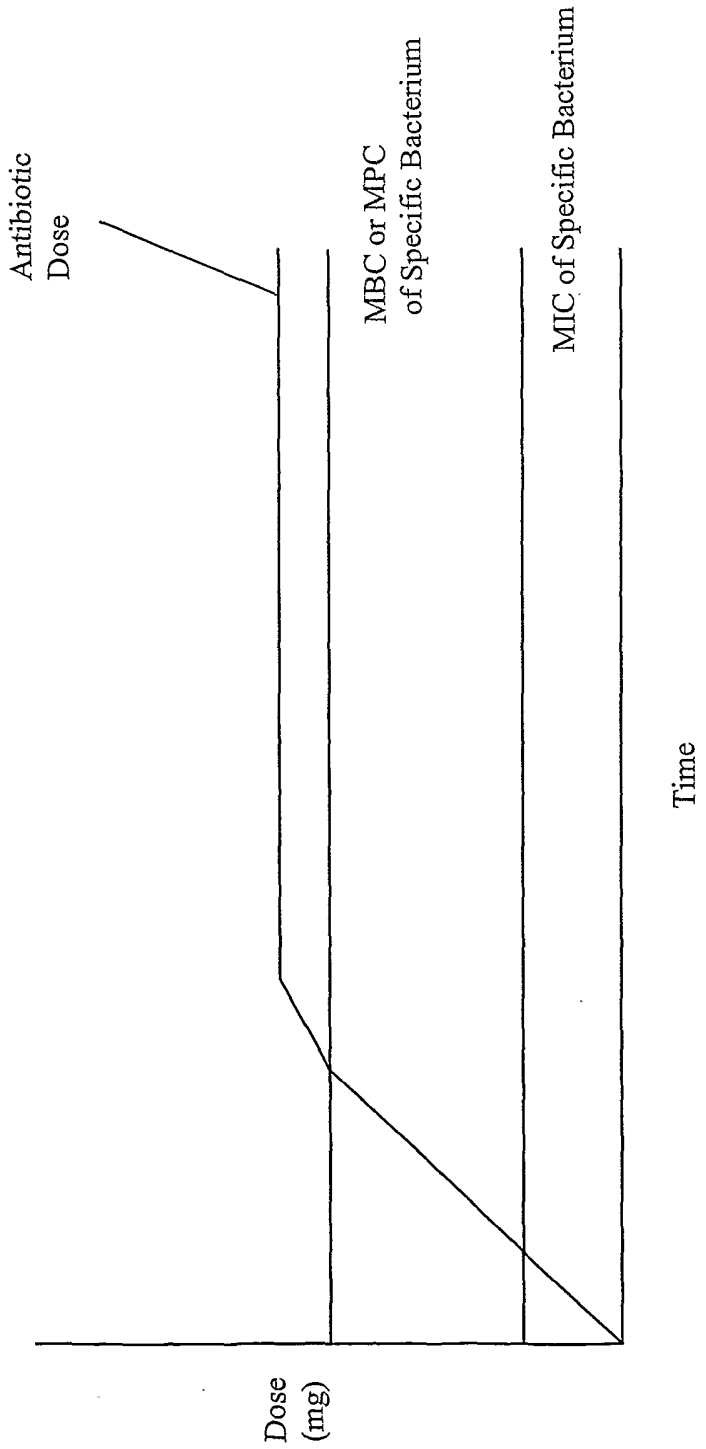
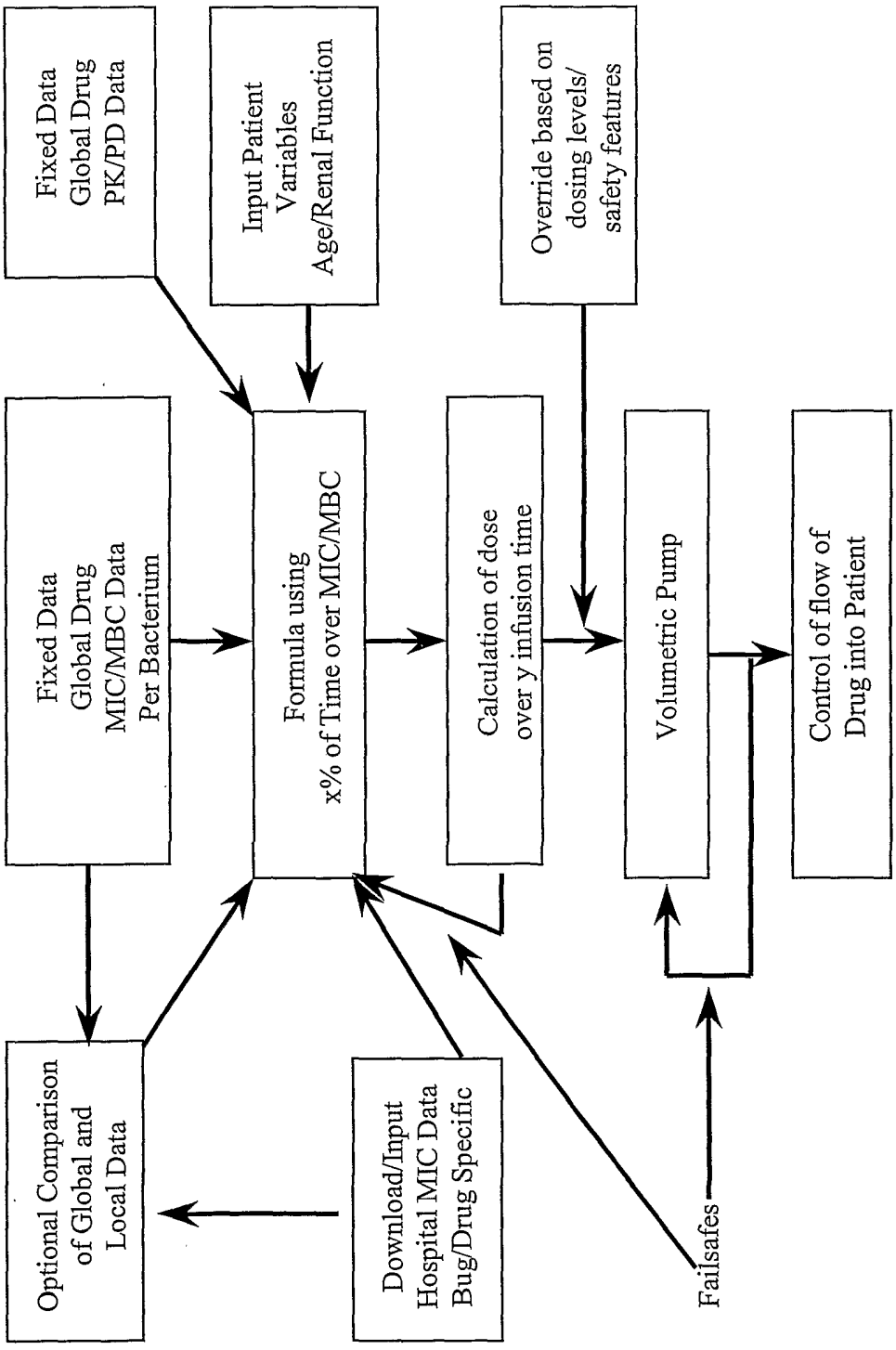

Antibiotic Dose
MBC or MPC of Specific Bacterium
MIC of Specific Bacterium
Time
Dose (mg)

Figure 3


Fixed Data Global Drug PK/PD Data
Input Patient Variables Age/Renal Function
Override based on dosing levels/ safety features
Fixed Data Global Drug MIC/MBC Data Per Bacterium
Formula using x% of Time over MIC/MBC
Calculation of dose over y infusion time
Volumetric Pump
Control of flow of Drug into Patient
Optional Comparison of Global and Local Data
Download/Input Hospital MIC Data Bug/Drug Specific
Failsafes

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02932

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/145

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 814 015 A (COWEN BARRY ET AL) 29 September 1998 (1998-09-29) column 4, line 8-19; figure 1 column 6, line 34 -column 7, line 5; figure 4 column 11, line 39-61 column 20, line 21 -column 21, line 11	1-14
X	US 6 039 251 A (CRONE AARON D ET AL) 21 March 2000 (2000-03-21) abstract	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2002	08/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rosenblatt, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/02932

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15,16,17
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted]onal Application No
PCT/GB 02/02932

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5814015 A	29-09-1998	AU 708108 B2	29-07-1999
		AU 4982096 A	11-09-1996
		EP 0813428 A1	29-12-1997
		JP 11500643 T	19-01-1999
		WO 9625963 A1	29-08-1996
US 6039251 A	21-03-2000	NONE	