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Utility of a Compatibility Chart for Continuous Infusions in the Intensive Care Unit

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Background: In the intensive care unit (ICU), multiple intravenous drugs are often administered through the same catheter line, greatly increasing the risk of drug incompatibility. We previously developed a compatibility chart including 27 drugs and have used it to avoid drug incompatibilities in the ICU. This retrospective study evaluated the utility of this chart by analyzing prescriptions and incidents of incompatibilities in an ICU.

Methods: We analyzed 257 ICU prescriptions of two or more continuous infusions on the same day during the period between March 2016 and February 2017 and investigated the rate of compliance with the compatibility chart. Drug combinations were classified as "compatible," "tolerable compatible," "incompatible," and "no data." For all combinations, the compliance rate was defined as the ratio of compatible and tolerable compatible combinations. Additionally, using our hospital incident report database, we analyzed 27,117 injections administered in the ICU between March 2016 and February 2017 and investigated incidents related to incompatibility.

Results: Three hundred infusion combinations were identified in the prescriptions. The compliance rate was 97% (n = 293). Of the 113 combinations judged to be tolerable compatible, 98% (n = 111) consisted of three or more continuous medications injected through the same intravenous line. Of the two incidents related to incompatibility in the incident report database, the combination "nicardipine and furosemide" was defined as incompatible in the compatibility chart.

Conclusions: The high rate of compliance with the compatibility chart suggested it was useful in preventing drug incompatibility. (J Nippon Med Sch 2022; 89: 227–232)

Key words: compatibility chart, intensive care unit, drug incompatibility, incident

Introduction

Patients admitted to intensive care units (ICUs) usually receive more medications by continuous intravenous infusion than do patients in general wards[1]. Thus, the risk of drug incompatibility is higher in the ICU. Therefore, it is important to adopt a safety approach that avoids drug incompatibility, especially in the ICU. Different techniques are used to avoid drug incompatibilities, such as changing administration time, flushing with normal saline before and after injection, and administration through another line. However, for continuous infusions, the only way to avoid drug incompatibility is to use a separate line for each drug.

The clinical pharmacist has the important responsibility of providing information about incompatible drugs. However, this task is time-consuming because the list of incompatible drugs differs between textbooks[2–5], and pharmacists may thus give information that differs in re-

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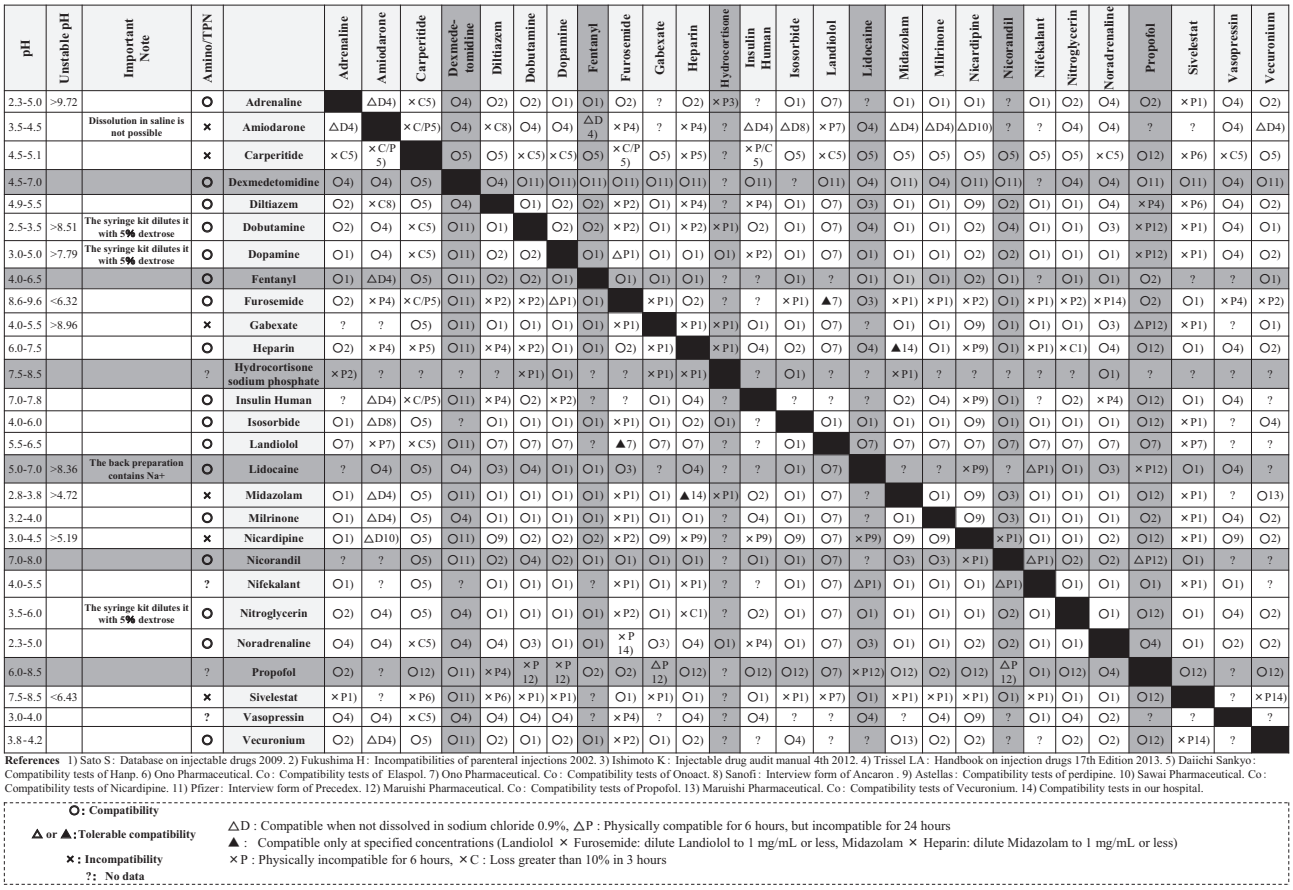

Fig. 1 The compatibility chart used in the Nippon Medical School Tama Nagayama Hospital.
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lation to the textbook used. For these reasons, compatibility charts are often created for hospital ICUs[1,6–8].

A compatibility chart summarizes the results of compatibility tests for the commonly used drugs in the ICU and can be used to quickly retrieve information on incompatible drugs. The utility of such charts has been demonstrated in questionnaire surveys for physicians and nurses[1,8]. However, the clinical usefulness of a compatibility chart when using mixtures of continuously injected drugs in the intravenous line is unknown. This study aimed to assess the utility of a compatibility chart in analyzing the status of prescriptions and incidents of drug incompatibilities in the ICU in catheter management.

Materials and Methods

Ethics

This study was approved by the Ethics Committee of Nippon Medical School Tama Nagayama Hospital (No. 409) and complied with the *Ethical Guidelines for Medical and Health Research Involving Human Subjects*.

Development and Management of the Compatibility Chart

The original compatibility chart for our hospital has been in use since 2013 and was revised in 2014 and 2015. The latest version of the chart contains 27 drugs (**Fig. 1**). These drugs are listed in rows and columns, and the results of compatibility tests are specified at the intersections. The chart contains information on drug names, standard pH, unstable pH, important information about the drugs, and incompatibility with infusions containing amino acids and total parenteral nutrition. Our chart was created by referring to drug compatibility reports published by pharmaceutical companies and textbooks on injectable drugs in Japan and the United States[2–5]. We classified the results as "compatible," "tolerable compatible," "incompatible," and "no data" (**Table 1**).

The developed chart was installed at several locations in the ICU, to allow easy access by the medical staff. The medical staff was advised to manage administration lines of continuous infusions in accordance with the chart. In addition, it was suggested that the staff inject intermit-

Table 1 Method for classifying drug incompatibility

	Display	Condition setting
Compatible	○	Physically compatible for 24 hours
		No loss of more than 10% in 3 hours
Tolerable compatible	△ D	Compatible when not dissolved in sodium chloride 0.9%
	△ P	Physically compatible for 6 hours, but incompatible for 24 hours (Only concentration of test higher than clinical dose)
	▲	Compatible only at specified concentrations
Incompatible	×P	Physically incompatible for 6 hours
	×C	Loss more than 10% in 3 hours
No data	?	No study available

tent infusions through other routes of continuous infusions. When various intermittent drugs were used, we suggested changing the administration time and avoiding mixing of intermittent infusions. Furthermore, drugs with a high risk of line blockage and turbidity when mixed with other drugs or solutions, such as potassium canrenoate, omeprazole, lansoprazole, bromhexine, amphotericin B, pazufloxacin, and daptomycin, are required to be flushed in sodium chloride 0.9% or dextrose 5% before and after administration. It was recommended that blood transfusions such as red blood cells, platelet concentrate, and fresh frozen plasma be administered alone, without being combined with injectable drugs other than sodium chloride 0.9%.

Use of Prescription Data to Evaluate the Compatibility Chart

This single-center retrospective observational study analyzed the medical prescriptions of 800 patients who were admitted to the ICU of Nippon Medical School Tama Nagayama Hospital between March 2016 and February 2017 and received two or more continuous infusions on the same day. Using patient data, we identified the prescription on the day when the maximum number of continuous infusions was administered during hospitalization and investigated the effect of mixing continuous injections within the same line.

Compliance with the compatibility chart and incidents related to incompatibility were used to evaluate the efficacy of intravenous line management. When two or more drugs were combined in the same line, we classified the combination, according to the compatibility chart, as "compatible," "tolerable compatible," "incompatible," and "no data." For combinations of three or more drugs in the same line, information on each drug was checked from the chart. If all the pairs were judged as compatible or tolerable compatible, the combination of three or more drugs was classified as tolerable compatible. We defined the combination of intermittent and continuous infusion as incompatible. Combinations not listed in this chart, except for intermittent and continuous combinations, were defined as no data. Additionally, we reassessed combinations classified as no data by using literature sources comprising drug compatibility reports that were similar to our chart. Inappropriate use of the compatibility chart was defined as incompatible, and no data of combination groups, and the compliance rate was defined as the ratio of compatible to tolerable compatible for all combination groups.

Use of Data on Incident Drug Incompatibilities to Evaluate the Compatibility Chart

Incidents of drug incompatibilities in the cumulative 27,117 injections administered in the ICU between March 2016 and February 2017 were reviewed. Combinations of intravenous infusion that resulted in problems such as intravenous line blockages and turbidity were also reviewed by using our hospital incident report database. The incident rate was defined as the ratio of the number of incidents to the cumulative total number of injections administered in our ICU. In addition, we examined whether incident cases could have been avoided by using the compatibility chart.

Results

Prescription Data

This study included 257 patients (mean age, 66.7 years; SD 16.1), and the total number of continuously injected drugs was 925. The mean duration from admission to the day when the analyzed prescriptions were written was 2.2 ± 3.4 days. **Table 2** shows the clinical characteristics of the patients. The mean number of continuously administered drugs per patient was 3.6 ± 1.4 (range, 2-9). In total, 231 patients (89.9%) received a combination of at least two continuous infusions through the same intravenous line, while 241 patients (93.8%) received intermit-

Table 2 Clinical characteristics of the patients

Characteristic	N = 257
Age, years, mean ± SD	66.7 ± 16.1
Central venous catheter (%)	131 (51.0)
Intubation (%)	172 (66.9)
Total number of continuous drugs administered	925
Number of continuous drugs administered per patient, mean ± SD	3.6 ± 1.4
Mean number of intravenous lines used for drug administration, mean ± SD	3.1 ± 0.8
Number of intermittent drugs administered (%)	241 (93.8)
Diagnosis	
Cerebrovascular disease (%)	83 (32.3)
Heart disease (%)	56 (21.8)
Infection (%)	24 (9.3)
Cardiopulmonary arrest (%)	21 (8.2)
Trauma (%)	21 (8.2)
Digestive disease (%)	20 (7.8)
Respiratory disease (%)	15 (5.8)
Central nervous disease (%)	12 (4.7)
Other (%)	5 (1.9)

SD = standard deviation

tent infusions. Three hundred combinations of drugs were classified into three groups, namely, combinations of two drugs (61.7%), combinations of three drugs (36.7%), and combinations of four drugs (1.6%); 1.0% were combinations of continuous infusion and intermittent infusion.

The 300 drug combinations were classified on the basis of our compatibility chart. The compliance rate, according to the compatibility chart, was 97% (n = 293). Of the 113 combinations judged to be tolerable compatible, 98% (n = 111) consisted of three or more continuously administered medicines injected through the same intravenous line. Of the five combinations judged to be incompatible, two ("propofol, midazolam, and diltiazem" and "hydrocortisone and heparin") were determined to be incompatible, based on the compatibility chart. The other combinations ("ozagrel and edaravone", "insulin human and sulbactam/ampicillin", and "insulin human and Albuminar") were judged incompatible because they were cases of coadministration of intermittent and continuous drugs. However, there were no documented issues with these incompatible combination prescriptions during clinical use.

The two combinations judged to be no data, namely, "midazolam and buprenorphine" and "ozagrel and heparin," have been re-evaluated in other studies and judged to be compatible combinations[3].

Data on Incident Drug Incompatibilities

There were two incidents related to drug incompatibility (incident rate, 0.0074%). The combination "nicardipine and furosemide" was defined as incompatible in our compatibility chart. The other (potassium canrenoate and Veen-D) was not listed in our compatibility chart.

Discussion

In this study, the usefulness of a compatibility chart was evaluated by analyzing its functionality in avoiding incompatibility of continuous drug infusions, as determined by compliance rate and incidents related to incompatibility. Our results showed that, according to the compatibility chart, the compliance rate of the drug combinations was high, and three or more drugs were sometimes administered through the same line. In addition, we found that four of the five incident cases could have been avoided with the help of the compatibility chart.

The high compliance rate (97%) of the combinations with the compatibility chart suggests that the compatibility chart can be used as a common reference tool for intravenous line management by ICU physicians, pharmacists, and nurses to avoid drug incompatibilities. Similar results were observed in studies that used questionnaires to evaluate the utility of compatibility charts. In those studies, 96%[1] and 91%[8] of nurses utilized the chart. The present study confirms the utility of compatibility charts in clinical practice.

Although intermittent infusions were used for 93.8% of the present patients, only three ("ozagrel and edaravone", "insulin human and sulbactam/ampicillin", and "insulin human and Albuminar") of the 300 drug combinations included were combinations of continuous and

intermittent infusions. We assume that intravenous line management was used to avoid, to the extent possible, combinations of continuous and intermittent infusions. Although the combinations "ozagrel and edaravone" and "insulin human and sulbactam/ampicillin" were both classified as compatible on the basis of drug compatibility test results[3], coadministration of continuous and intermittent infusions carries the risk of rapid administration of a continuous drug within the route. For instance, a bolus glucose solution accidentally injected into a line for adrenaline resulted in bolus administration of adrenaline and ventricular fibrillation in a patient[9]. In addition, intermittent drugs have a high risk of drug incompatibilities. In a retrospective observational study conducted in Brazil, 95% of infusions administered in the ICU that caused incompatibilities were reported to contain intermittent infusions[10]. Therefore, to avoid incompatibilities, it is necessary not only to create a compatibility chart but also to avoid combinations of intermittent infusions whenever possible.

The two cases of ozagrel combination (ozagrel and edaravone; ozagrel and heparin) were included as continuous injectable drugs not listed on our compatibility chart. Continuous administration of ozagrel is used to treat subarachnoid hemorrhage (SAH)[11]. Because we regularly treat patients with SAH in our ICU, ozagrel is used frequently and should thus be added to the list of drugs on our compatibility chart. Similarly, previous studies reported that inclusion of drugs on the compatibility chart should be based on usage frequency of injectable drugs in the hospital and clinical department in question[6,7]. Moreover, we recommend a periodic review of the types of drugs in the compatibility chart.

Although there were two incompatible combinations ("propofol, midazolam, and diltiazem", and "hydrocortisone and heparin"), as indicated by the compatibility chart, there were no documented issues (such as route blockage) with these combinations during clinical use. This could be attributable to the fact that there was no precipitation observed for these combinations, as the actual administered concentration of the drugs differed from that in the compatibility test. Alternatively, smaller precipitates might have been overlooked, as the minimum particle size visible to the human eye is 40 μm[12]. Moreover, it is difficult to identify incompatibility because propofol is a white-colored fat emulsion. For these reasons, these two incompatible combinations require reassessment via a compatibility test.

There were two incidents related to incompatibilities investigated in the incident report (incident rate, 0.0074%). Our incident rate was similar to that of another hospital using a compatibility chart (0.0025%)[8]. The incompatibility combination of nicardipine and furosemide was defined as incompatible in our compatibility chart, and it was assumed that this incident could have been avoided. While the combination of potassium canrenoate and Veen-D is not listed in our compatibility chart, flushing in sodium chloride before and after administration is required in our hospital. Therefore, this case could have been avoided if the drugs had been administered in compliance with our hospital rules. In our ICU, prescription inputs are handwritten and do not rely on an ordering system or electronic medical record system. In the future, when these systems are introduced to our ICU, we will consider creating a system that can alert us to incompatible combinations or ways to avoid incompatibility at the time of prescription.

Although the compliance rate according to the compatibility chart was high, 38.3% of the combinations included three or more drugs. A previous study in the pediatric ICU reported that 68.7% of combinations included three or more drugs[13]. Drug compatibility studies are mostly performed between two drugs[14–16]. The American Society of Health-System Pharmacists cautions that compatibility information should not be misinterpreted to apply to more than the two specific agents under the conditions of the study[17]. Therefore, in clinical practice, determining the compatibility of three or more medicines may not be accurate because it is only an estimate based on drug compatibility tests of any two drugs in the combination and not an actual drug compatibility test[13]. Accordingly, to reduce the risk of incompatibility, we suggest that the safety of a mixture of more than two drugs be evaluated by conducting drug compatibility tests between the individual drugs in the mixture.

There were some limitations to this study. First, our compatibility chart referred only to studies that evaluated physical compatibility. Hence, we did not evaluate the chemical compatibility of drugs used in the ICU, because of the limited information. A recent systematic review found that physical and/or chemical compatibility data existed for 54% of the 820 two-drug combinations of 41 commonly used drugs in the ICU and that chemical compatibility data existed for only 9% of combinations[18]. Thus, a combination judged to be compatible in our compatibility chart could be chemically incompatible. Second, although our compatibility chart contains abundant data on branded drugs, our hospital preferentially uses ge-

neric drugs. Thus, unexpected incompatibilities might occur because of differences in pharmaceutical additives. Therefore, when unexpected incompatibilities occur, we should investigate the cause and revise our compatibility chart accordingly.

In this study, the high compliance rate of the compatibility chart suggested that it could be used as a valuable reference tool to avoid drug incompatibility. To use this chart effectively, it is important, to the extent possible, not to mix intermittent infusions. In addition, because 38.3% of the present combinations included three or more drugs administered in the same line, we recommend that multi-drug compatibility tests should be conducted, to avoid the risk of incompatibility. In the future, we plan to conduct multi-drug compatibility tests and provide updated data on drug compatibility.

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Conflict of Interest: The authors declare no conflicts of interest.

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